Development of a Scalable and Sustainable Continuous-Flow Microreaction Process for Mononitration of Aromatic Compounds with High Selectivity and Yield

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Supplementary information

Contents:

1. Materials and Methods

1.1. General Information

All chemicals were obtained from standard commercial suppliers and used as received without further purification. Flash column chromatography was performed on silica gel (300–400 mesh). ¹H NMR chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS) as an internal standard, with solvent resonance peaks (e.g., CDCl$_3$ at 7.26 ppm, DMSO-d6 at 2.50 ppm) used for calibration. Product analysis and purity confirmation were conducted using Shimadzu GC-2014 for gas chromatography (GC) or Agilent 1260 for high-performance liquid chromatography (HPLC). Final products were purified through flash column chromatography on silica gel and characterized by ¹H NMR spectroscopy.

1.2. Continuous-Flow Reactor Setup

In the condition optimization and substrate expansion phases, the Corning Advanced-Flow Reactor (AFR) Lab reactor was employed. The Lab reactor consists of plunger pumps, a heat exchanger, and a single fluidic module. This fluidic module is composed of four confined structured hybrid glass layers, which create three flow zones: a reaction zone (with a volume of 2.7 mL) sandwiched between two heat transfer zones. The fluidic module has dimensions of 155 × 125 × 8 mm. The connection between the plunger pumps and the microreactor is made using PFA tubing (1/8 inch outer diameter). The recommended flow rate range for this setup is 0 to 9.9 mL min^{-1}.

For the scale-up experiments, the Corning Advanced-Flow Reactor (AFR) G1 reactor setup was used, consisting of plunger pumps, a heat exchanger, and five fluidic modules. Each fluidic module comprises four confined structured hybrid glass layers, creating three flow zones: a reaction zone (with a volume of 8.3 mL) sandwiched between two heat transfer zones, with an area-to-volume ratio of 788.5 m^{-1}. The internal diameter of the reaction channels ranges from 1 mm at the narrowest point to 1 cm at the widest point. Connections between the plunger pumps and the microreactor were made with PFA tubing (1/4 inch outer diameter). The recommended flow rate range for this system is 10 to 200 mL min^{-1}.

1.3. General Procedure for Condition Optimization of Continuous Nitration

The concentrated H$_2$SO$_4$ (98%) was mixed with a known quantity of ice-cold water to achieve the required concentration of sulfuric acid. The diluted H$_2$SO$_4$ was then combined with a known amount of HNO$_3$ (98%) to prepare the mixed acid with the desired molar ratio. The two reactants (p-xylene and the mixed acid) were pumped into a continuous reactor via plunger pumps, where they reacted under controlled flow rate and temperature conditions. Samples were collected at the reactor outlet and immediately quenched with a fixed amount of ice-cold water. A known volume of DCM was added to extract the organic phase from the samples. The organic phase was washed twice with water and separated by gravity. It was then washed with brine to remove any residual water. The final samples were analyzed using gas chromatography with an HP5 capillary column and a flame ionization detector

(FID).

1.4. Laboratory-Scale Continuous-Flow Nitration Procedure of *p*-Xylene

A 98% concentrated H_2SO_4 solution was diluted with ice water to prepare a 70% H_2SO_4 solution, which was subsequently combined with 98% concentrated HNO_3 (fuming nitric acid, FNA) to produce a mixed acid with a molar ratio of H_2SO_4 to HNO_3 of 1.6. The resulting mixed acid solution contained 9.16 mol L^{-1} H_2SO_4 and 5.72 mol L^{-1} HNO_3.

The reaction feedstock (*p*-xylene) and the mixed acid were introduced into the Corning Advanced-Flow Lab Reactor using pumps A and B, operating at flow rates of 1.17 mL min^{-1} and 7.25 mL min^{-1}, respectively. The two streams combined in the first fluidic module before passing through a single reaction module. The reaction was carried out at 60 °C with a residence time of 19 seconds. The resulting reaction mixture was collected and immediately quenched with ice water.

The organic phase was extracted using a known volume of CH_2Cl_2, followed by two sequential washes with deionized water and gravity separation. Residual water in the organic phase was removed by washing with a saturated brine solution. Finally, the purified samples were analyzed via gas chromatography (GC) equipped with an HP5 capillary column (30 m × 0.25 mm, 0.25 μm film thickness) and a flame ionization detector (FID).

1.5. Laboratory-Scale Continuous-Flow Nitration Procedure of *o*-Xylene

A 98% concentrated H_2SO_4 solution was diluted with ice water to prepare a 70% H_2SO_4 solution, which was subsequently combined with 98% concentrated HNO_3 (fuming nitric acid, FNA) to produce a mixed acid with a molar ratio of H_2SO_4 to HNO_3 of 1.6. The resulting mixed acid solution contained 9.16 mol L^{-1} H_2SO_4 and 5.72 mol L^{-1} HNO_3.

The reaction feedstock (*o*-xylene) and the mixed acid were introduced into the Corning Advanced-Flow Lab Reactor using pumps A and B, operating at flow rates of 1.14 mL min^{-1} and 7.25 mL min^{-1}, respectively. The two streams combined in the first fluidic module before passing through a single reaction module. The reaction was carried out at 80 °C with a residence time of 19 seconds. The resulting reaction mixture was collected and immediately quenched with ice water.

The organic phase was extracted using a known volume of CH_2Cl_2, followed by two sequential washes with deionized water and gravity separation. Residual water was further removed by washing the organic phase with a saturated brine solution. Finally, the purified samples were analyzed via gas chromatography (GC) equipped with an HP5 capillary column (30 m × 0.25 mm, 0.25 μm film thickness) and a flame ionization detector (FID).

1.6. Laboratory-Scale Continuous-Flow Nitration Procedure of Chlorobenzene

A 98% concentrated H_2SO_4 solution was diluted with ice water to prepare a 70% H_2SO_4 solution, which was subsequently combined with 98% concentrated HNO_3 (fuming nitric acid, FNA) to produce a mixed acid with a molar ratio of H_2SO_4 to HNO_3 of 1.6. The resulting mixed acid solution contained 9.16 mol L^{-1} H_2SO_4 and 5.72 mol L^{-1} HNO_3.

The reaction feedstock (chlorobenzene) and the mixed acid were introduced into the Corning

Advanced-Flow Lab Reactor using pumps A and B, operating at flow rates of 0.90 mL min^{-1} and 6.83 mL min^{-1}, respectively. The two streams combined in the first fluidic module before passing through a single reaction module. The reaction was carried out at 100 °C with a residence time of 21 seconds. The resulting reaction mixture was collected and immediately quenched with ice water.

The organic phase was extracted using a known volume of CH_2Cl_2, followed by two sequential washes with deionized water and gravity separation. Residual water in the organic phase was removed by washing with a saturated brine solution. Finally, the purified samples were analyzed via gas chromatography (GC) equipped with an HP5 capillary column (30 m × 0.25 mm, 0.25 µm film thickness) and a flame ionization detector (FID).

1.7. Laboratory-Scale Continuous-Flow Nitration Procedure of Toluene

A 98% concentrated H_2SO_4 solution was diluted with ice water to prepare a 70% H_2SO_4 solution, which was subsequently combined with 98% concentrated HNO_3 (fuming nitric acid, FNA) to produce a mixed acid with a molar ratio of H_2SO_4 to HNO_3 of 1.6. The resulting mixed acid solution contained 9.16 mol L^{-1} H_2SO_4 and 5.72 mol L^{-1} HNO_3.

The reaction feedstock (toluene) and the mixed acid were introduced into the Corning Advanced-Flow Lab Reactor using pumps A and B, operating at flow rates of 1.15 mL min^{-1} and 8.36 mL min^{-1}, respectively. The two streams combined in the first fluidic module before passing through a single reaction module. The reaction was carried out at 70 °C with a residence time of 17 seconds. The resulting reaction mixture was collected and immediately quenched with ice water.

The organic phase was extracted using a known volume of CH_2Cl_2, followed by two sequential washes with deionized water and gravity separation. Residual water in the organic phase was further removed by washing with a saturated brine solution. Finally, the purified samples were analyzed via gas chromatography (GC) equipped with an HP5 capillary column (30 m × 0.32 mm, 0.25 µm film thickness) and a flame ionization detector (FID).

1.8. Laboratory-Scale Continuous-Flow Nitration Procedure of Ethyl 3,4-bis (2-methoxyethoxy) benzoate

A 70% H_2SO_4 solution was prepared by diluting concentrated sulfuric acid (98%) with ice water and subsequently mixing it with concentrated nitric acid (fuming nitric acid, FNA) to obtain a mixed acid with a molar ratio of H_2SO_4 to HNO_3 of 1.6, yielding a composition of 9.16 mol L^{-1} H_2SO_4 and 5.72 mol L^{-1} HNO_3. Separately, 10 g of ethyl 3,4-bis (2-methoxyethoxy) benzoate was dissolved in 20 mL of dichloromethane, producing a solution with a density of 1.82 g mL^{-1} and a mass fraction of 27%. The reaction feedstock, and the mixed acid were introduced into the Corning Advanced-Flow Lab Reactor using pumps A and B at flow rates of 1.15 mL min^{-1} and 1.33 mL min^{-1}, respectively. The two streams combined in the first fluidic module before passing through a single reaction module. The reaction was carried out at 30 °C with a residence time of 65 seconds. The resulting reaction mixture was collected and immediately quenched with ice water.

The reaction products were collected at the reactor outlet and immediately quenched with ice water. The resulting mixture was subjected to liquid-liquid extraction using dichloromethane (CH_2Cl_2) to separate the organic phase, followed by two washes with water and gravity separation. Residual

water in the organic phase was removed by washing with a saturated brine solution. Finally, the samples were analyzed using high-performance liquid chromatography (HPLC) equipped with a C18 column.

1.9. Pilot-Scale Nitration Procedure for *p*-Xylene

A 98% concentrated H_2SO_4 solution was diluted with ice water to prepare a 70% H_2SO_4 solution, which was subsequently combined with 98% concentrated HNO_3 (fuming nitric acid, FNA) to produce a mixed acid with a molar ratio of H_2SO_4 to HNO_3 of 1.6. The resulting mixed acid solution contained 9.16 mol L^{-1} H_2SO_4 and 5.72 mol L^{-1} HNO_3.

The reaction feedstock (*p*-xylene) and the mixed acid were introduced into the Corning Advanced-Flow G1 Reactor using pumps A and B at flow rates of 11.67 mL min^{-1} and 72.52 mL min^{-1}, respectively. The two streams merged in the first fluidic module and then passed sequentially through five reaction modules. The reaction was carried out at 60 °C with a residence time of 29 seconds. The resulting reaction mixture was collected at the reactor outlet and immediately quenched with ice water.

The organic phase was extracted using a known volume of CH_2Cl_2, followed by two sequential washes with deionized water and gravity separation. Residual water in the organic phase was removed by washing with a saturated brine solution. Finally, the purified samples were analyzed via gas chromatography (GC) equipped with an HP5 capillary column (30 m × 0.25 mm, 0.25 μm film thickness) and a flame ionization detector (FID).

1.10. Pilot-Scale Nitration Procedure for *o*-Xylene

A 98% concentrated H_2SO_4 solution was diluted with ice water to prepare a 70% H_2SO_4 solution, which was subsequently combined with 98% concentrated HNO_3 (fuming nitric acid, FNA) to produce a mixed acid with a molar ratio of H_2SO_4 to HNO_3 of 1.6. The resulting mixed acid solution contained 9.16 mol L^{-1} H_2SO_4 and 5.72 mol L^{-1} HNO_3.

The reaction feedstock (*o*-xylene) and the mixed acid were introduced into the Corning Advanced-Flow G1 Reactor using pumps A and B at flow rates of 11.38 mL min^{-1} and 72.52 mL min^{-1}, respectively. The two streams merged in the first fluidic module and then passed sequentially through five reaction modules. The reaction was carried out at 60 °C with a residence time of 29 seconds. The resulting reaction mixture was collected at the reactor outlet and immediately quenched with ice water.

The organic phase was extracted using a known volume of CH_2Cl_2, followed by two sequential washes with deionized water and gravity separation. Residual water in the organic phase was removed by washing with a saturated brine solution. Finally, the purified samples were analyzed via gas chromatography (GC) equipped with an HP5 capillary column (30 m × 0.25 mm, 0.25 μm film thickness) and a flame ionization detector (FID).

## 2. Characterization data

2,5-Dimethylnitrobenzene (**1b**)
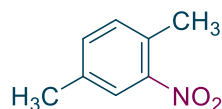
94.6% yield; Yellow transparent liquid; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.77 (s, 1H), 7.30 (d, J = 6.9 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 2.54 (s, 3H), 2.39 (s, 3H). All analytical data were in good accordance with data reported in the literature [S1].

2,3-Dimethylnitrobenzene (**2b**)
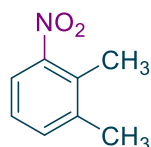
97.6% yield; Yellow transparent liquid; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.59 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.19 (t, J = 7.9 Hz, 1H), 2.37 (d, J = 2.9 Hz, 6H). All analytical data were in good accordance with data reported in the literature [S1].

3,4-Dimethylnitrobenzene (**2c**)
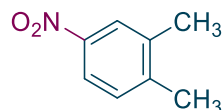
97.6% yield; Yellow transparent liquid; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.99 (d, J = 2.5 Hz, 1H), 7.94 (dd, J = 8.3, 2.5 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 2.36 (s, 6H). All analytical data were in good accordance with data reported in the literature [S1].

2-Chloronitrobenzene (**3b**)
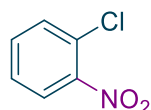
64.7% yield; Yellow crystal; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.87 (dd, J = 8.0, 1.6 Hz, 1H), 7.61 – 7.48 (m, 2H), 7.42 (m, 1H). All analytical data were in good accordance with data reported in the literature [S2].

4-Chloronitrobenzene (**3c**)
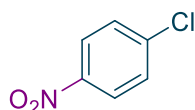
34.7% yield; Yellow crystal; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.19 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H). All analytical data were in good accordance with data reported in the literature [S3].

o- Nitrotoluene (**4b**)
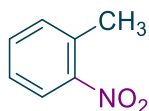
61.6% yield; Yellow transparent liquid; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.34 (d, *J* = 4.8 Hz, 2H), 2.60 (s, 3H). All analytical data were in good accordance with data reported in the literature [S4].

p-Nitrotoluene (**4c**)
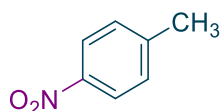
39.4% yield; Yellow transparent liquid; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.11 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 2.47 (s, 3H). All analytical data were in good accordance with data reported in the literature [S5].
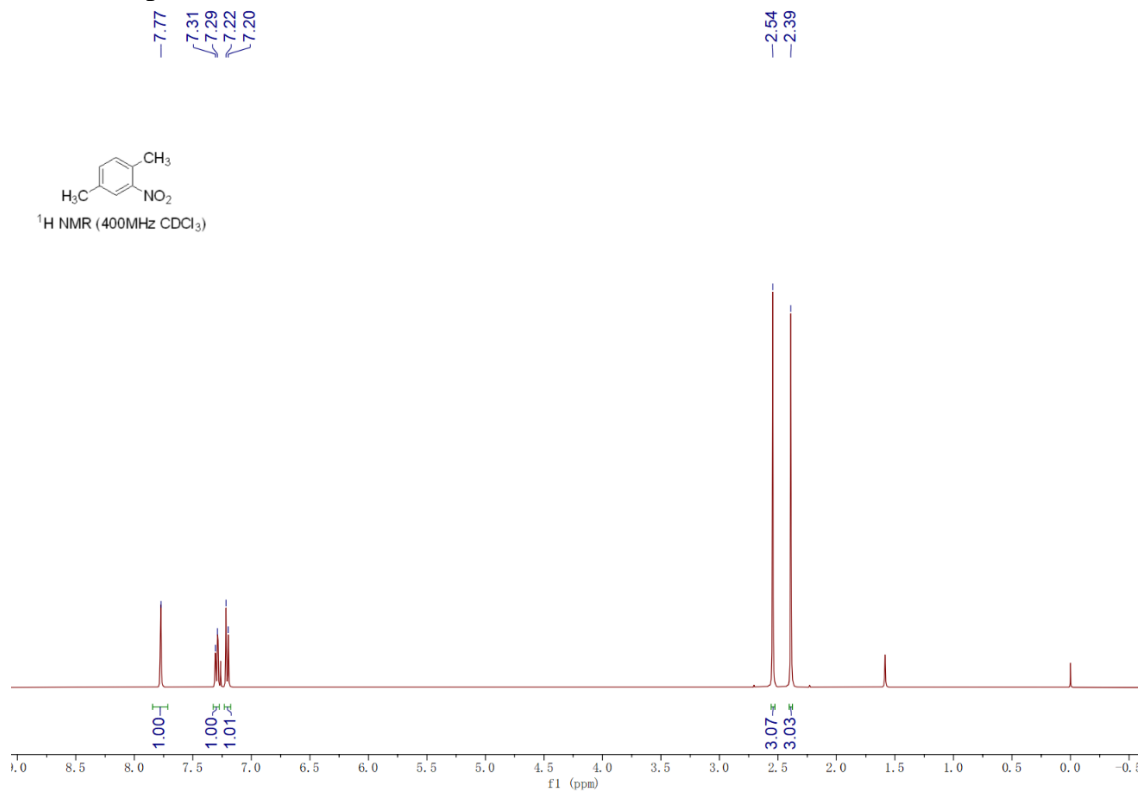
Ethyl 4,5-bis(2-methoxyethoxy)-2-nitrobenzoate (**5b**)
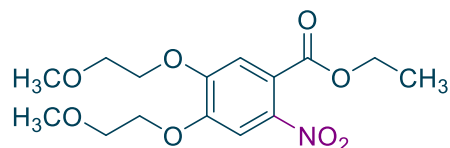
99.3% yield; Yellow oil; **^{1}H NMR** (**400 MHz, CDCl$_3$**) δ 7.44 (s, 1H), 7.07 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.19 (q, *J* = 4.7 Hz, 4H), 3.74 (t, *J* = 4.5 Hz, 4H), 3.39 – 3.33 (m, 6H), 1.27 (t, *J* = 7.1 Hz, 3H). All analytical data were in good accordance with data reported in the literature [S6].
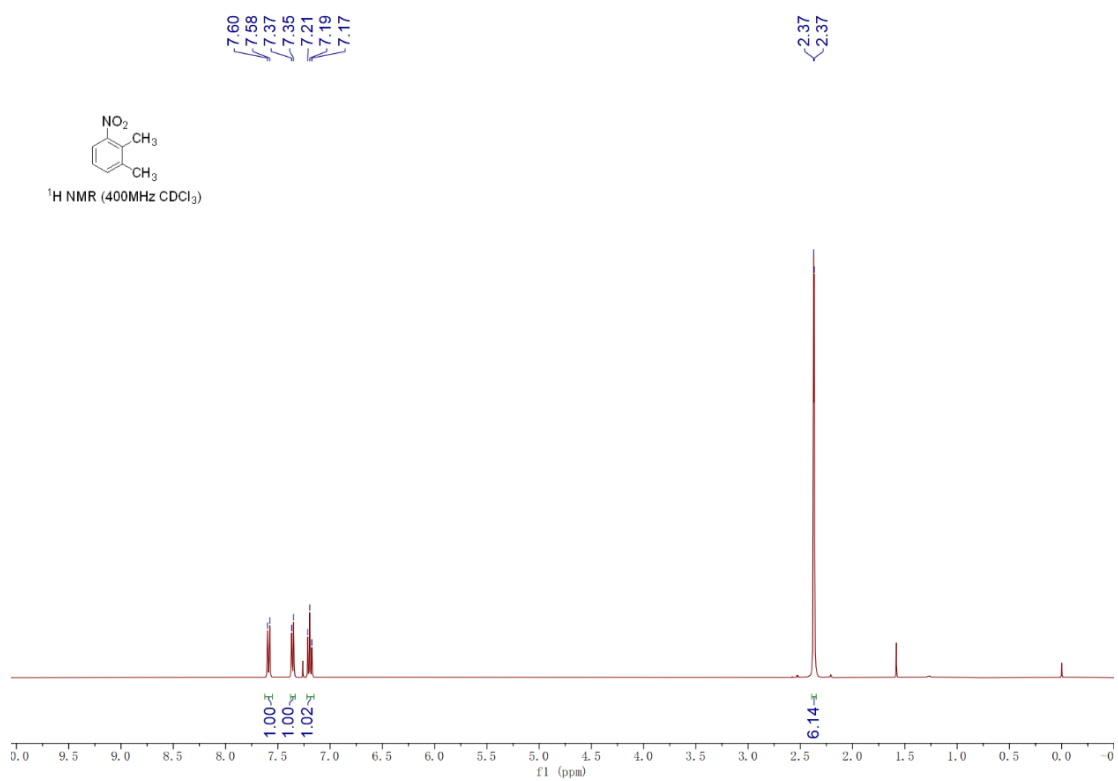
3. References

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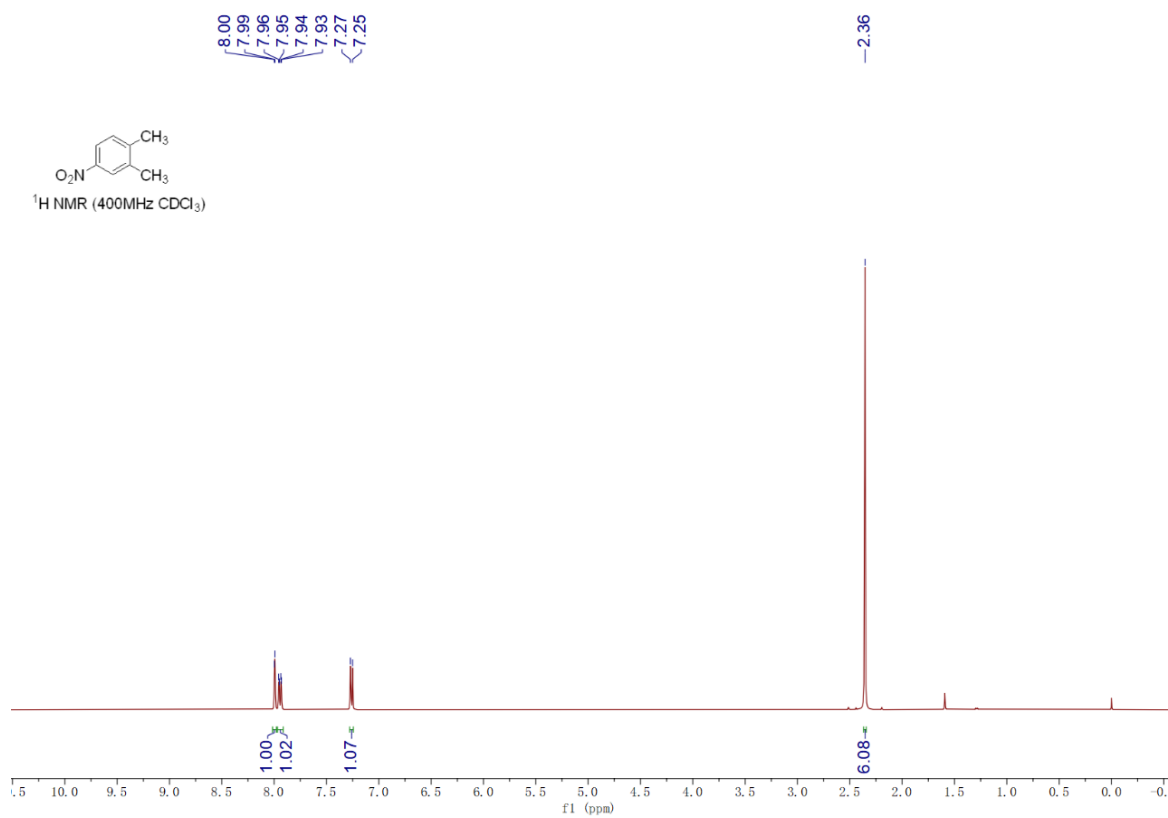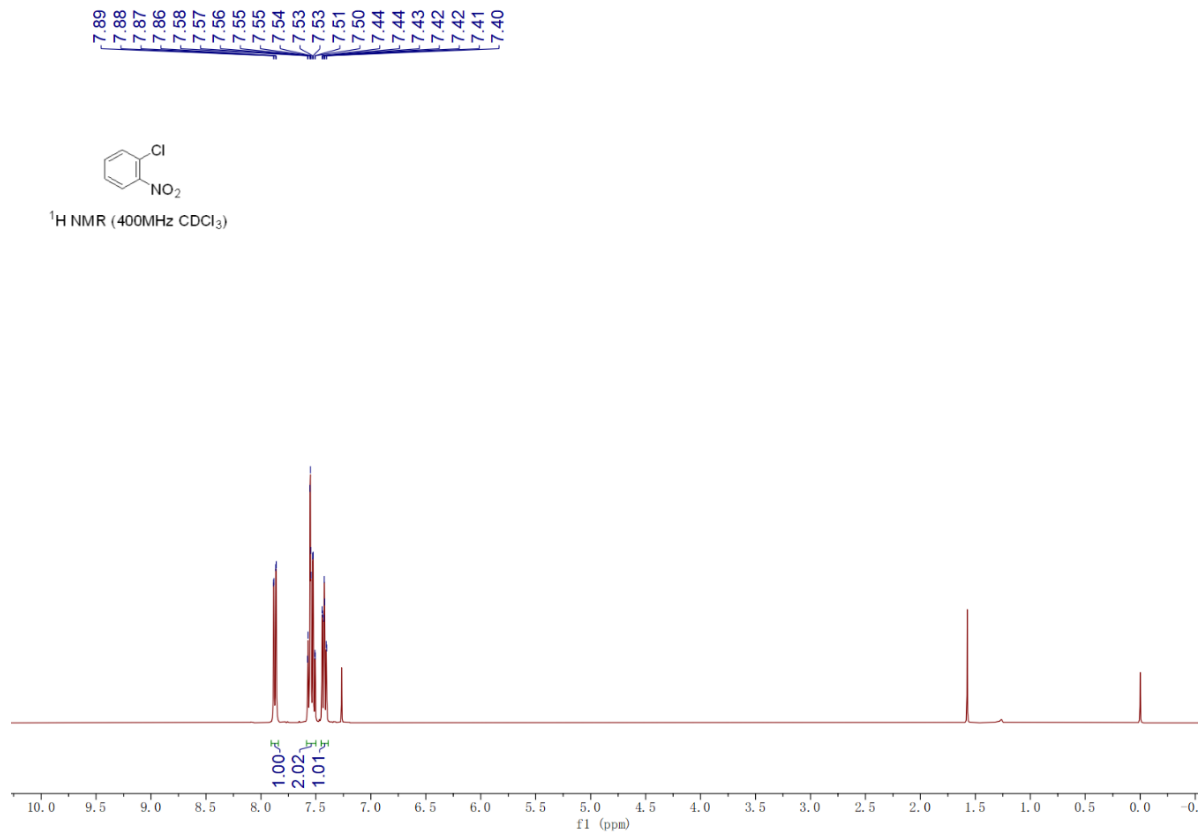
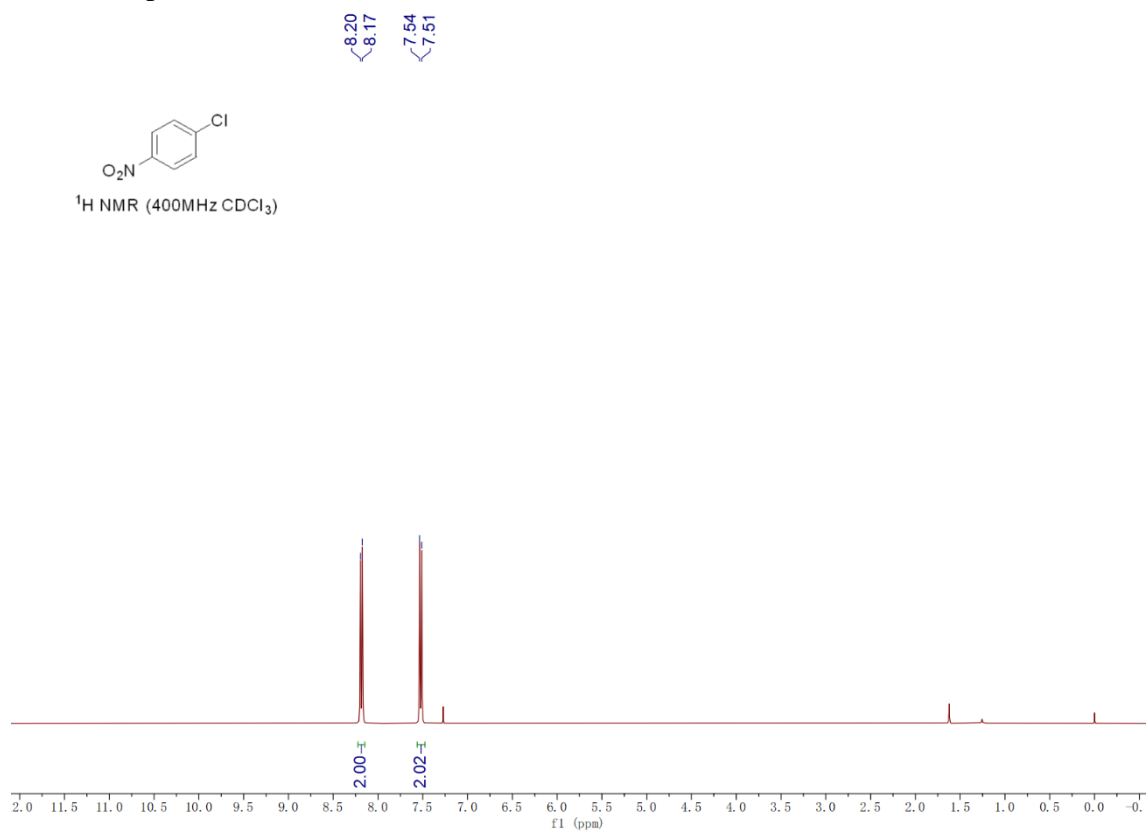# 4. Spectra

^{1}H NMR spectra of **1b**

^{1}H NMR (400MHz CDCl$_3$)

^{1}H NMR spectra of **2b**

^{1}H NMR (400MHz CDCl$_3$)

¹H NMR spectra of **2c**

¹H NMR (400MHz CDCl₃)

8.00
7.99
7.96
7.95
7.94
7.93
7.27
7.25

−2.36

1.00
1.02
1.07
6.08

f1 (ppm)

¹H NMR spectra of **3b**

¹H NMR (400MHz CDCl₃)

7.89
7.88
7.87
7.86
7.58
7.57
7.56
7.55
7.54
7.53
7.53
7.51
7.50
7.44
7.43
7.42
7.42
7.41
7.40

1.00
2.02
1.01

f1 (ppm)

^{1}H NMR spectra of **3c**

8.20
8.17
7.54
7.51

^{1}H NMR (400MHz CDCl$_3$)

2.00
2.02

2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

^{1}H NMR spectra of **4b**

7.97
7.95
7.52
7.51
7.50
7.49
7.48
7.36
7.35
7.34
7.33
7.32
7.32

2.60

^{1}H NMR (400MHz CDCl$_3$)

1.01
1.05
2.03
3.02

.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
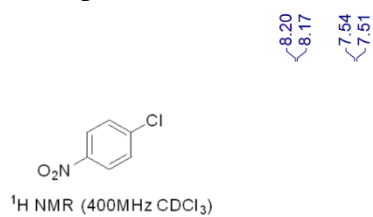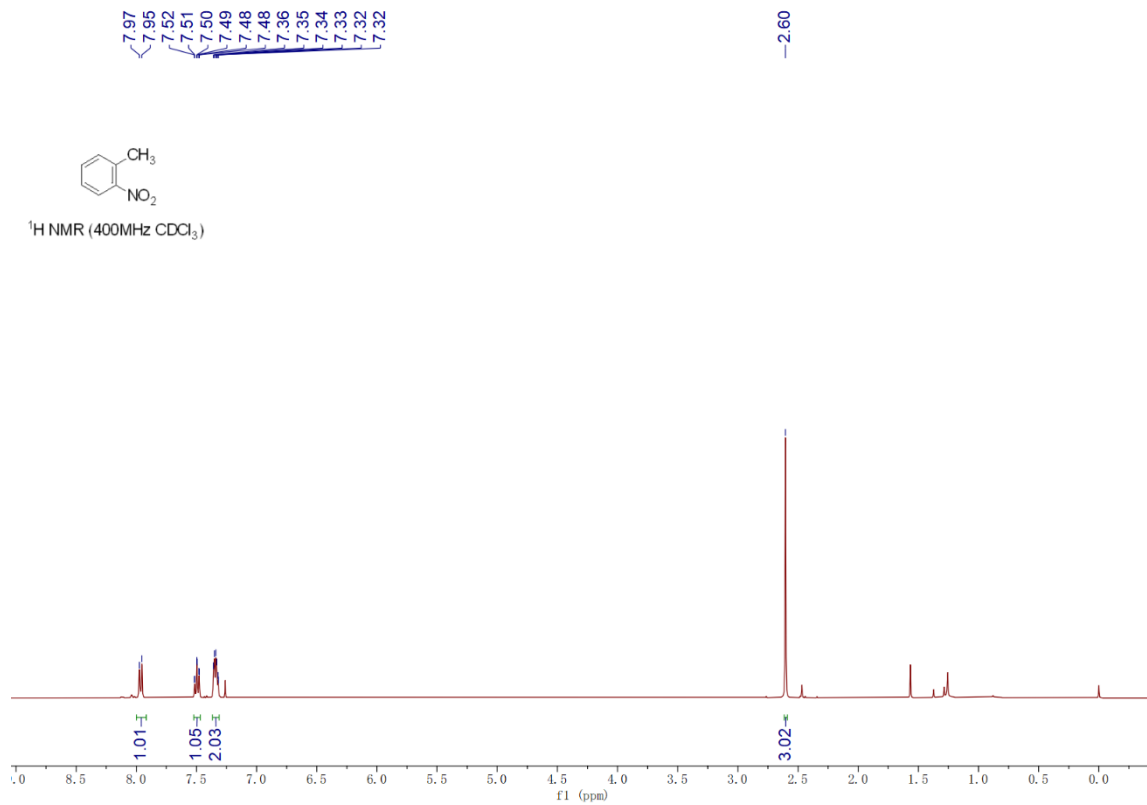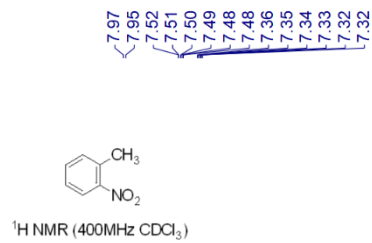
^{1}H NMR spectra of **4c**

^{1}H NMR (400MHz CDCl$_3$)

8.13
8.10
7.33
7.31
2.47

1.98
2.00
3.07

f1 (ppm)

^{1}H NMR spectra of **5b**

^{1}H NMR (400MHz CDCl$_3$)

7.44
7.07
4.32
4.30
4.28
4.26
4.20
4.19
4.18
4.17
3.75
3.74
3.73
3.38
3.38
1.29
1.27
1.26

1.00
1.00
2.14
4.04
4.06
6.00
3.07

f1 (ppm)