CORNING

Advanced-Flow™ Reactors

Nitration of phenol in flow

Application Note #8
Issued: July 2022

Aim: The objective of this experiment is to perform a nitration reaction and study the effect of different parameters (Temperature, flow rate, stoichiometry etc.).

Setup: Nebula™ Unit or Corning® Lab Reactor and its dosing module and chillers.

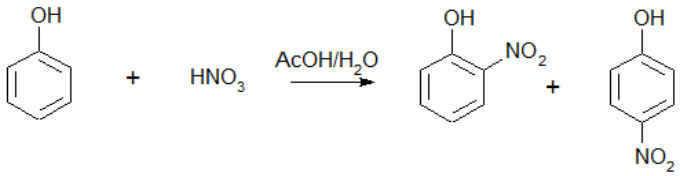


Figure 1: Nitration of phenol

Analytics: GC to determine the ratio of each isomer (ortho/para)

Safety:
Make sure you read the MSDS of the chemicals and the safety notes in the Manual. Keep the Reactor under a ventilated fumehood and wear appropriate personal protective equipment. Beware: Nitric acid tends to react very energetically with many organic compounds. It is typically not compatible with Ethanol, Acetone, alcohols….

Feed Preparation:
Feed1: Phenol (4.7 g, 50 mmol) are dissolved in 25 ml of glacial acetic acid.
Feed 2: HNO_3 (5.4 mL, 79 mmol, 65%) is dissolved in 25 ml of water (Exothermic: slowly add acid to water!).

Flow experiment:
Put inert alkane in the back of the piston pump as safety before starting to run the equipment.
Each feed is pumped at 1 ml/min through the module, for a combined flowrate of 2 ml/min. The temperature and flow rate can be varied to study their effect on conversion (an adequate thermostat must be on at all time).
N.B: A black suspension is formed gradually at the outlet, likely due to expected polymerization. Extra HNO_3 equivalent can reduce the polymerization. To clean the system, flush the system (description next session).

Cleaning: **(Beware: the reaction of acid with water is very exothermic and could damage the equipment or cause injury!)** After putting inert alkane in the back of the piston pump, flash the feed tubing with Nitrogen for 5 min. Replace the feed solutions with water and let each pump run at 1 ml/min for at least 20 minutes. Swap the inlet solutions with acetic acid and rinse for 20 min at 1ml/min per pump to remove any dark traces. Swap the solvent for isopropanol before switching the system off.

NB: In case of partial clogging, rinse with water for 10 min and then acetic acid.

Work-up: The collected solution (*ca* 18 ml in 9 min) is diluted with 50 ml of water. The organic phase is extracted with dichloromethane (2 x 25 ml). The organic phase solvent is then removed under vacuum (rotary evaporator). Steam distillation can then be used to separate both isomers (160°C).

Results: Visible effect on the reaction:

1) Temperature: It might be possible to see nitric acid evaporation in the reactor due to the exotherm. Its impact and disruption on the system is worth checking.
2) The conversion also tends to be higher with more residence time.
3) The Ortho/para isomer ratio is affected by the temperature and reduced residence time (cf figure 2).

4) After steam distillation, using condition of Entry 10, 35 % of o-nitrophenol (yellow solid) and 12 % of p-nitrophenol (brown solid) can be collected, whereas the reported yield in batch is respectively 30% and 10% (Organikum, Ed 19 ,**1993**, p321-322).
5) Under the condition at 60 °C and 1 ml/min, the pattern of the microreactor is continuous and homogenous and the preliminary material has the total conversion.

Entry	T/°C	Combined Flowrate	Full conversion	A_{ortho}/A_{para}	Picture
1	20	0.5 ml/min	No	2.9	
2	20	1 ml/min	No	3.35	
3	20	1.5 ml/min	No	1.62	
4	40	0.5 ml/min	Yes	2.57	(a)
5	40	1 ml/min	Yes	2.78	(b)
6	40	1.5 ml/min	Yes	3.16	(c)
7	40	2 ml/min	No	3.16	(d)
8	40	4 ml/min	No	3.88	
9	60	0.5 ml/min	Yes	2.66	(e)
10	60	1 ml/min	Yes	2.7	(f)
11	60	1.5 ml/min	Yes	3.05	(g)
12	60	2 ml/min	Yes	3.2	(h)
13	80	0.5 ml/min	Yes	3.05	(i)
14	80	1 ml/min	Yes	5.34	(j)
15	80	1.5 ml/min	Yes	2.56	(k)
16	80	2 ml/min	Yes	2.88	(l)

Figure 2: Table of tested conditions

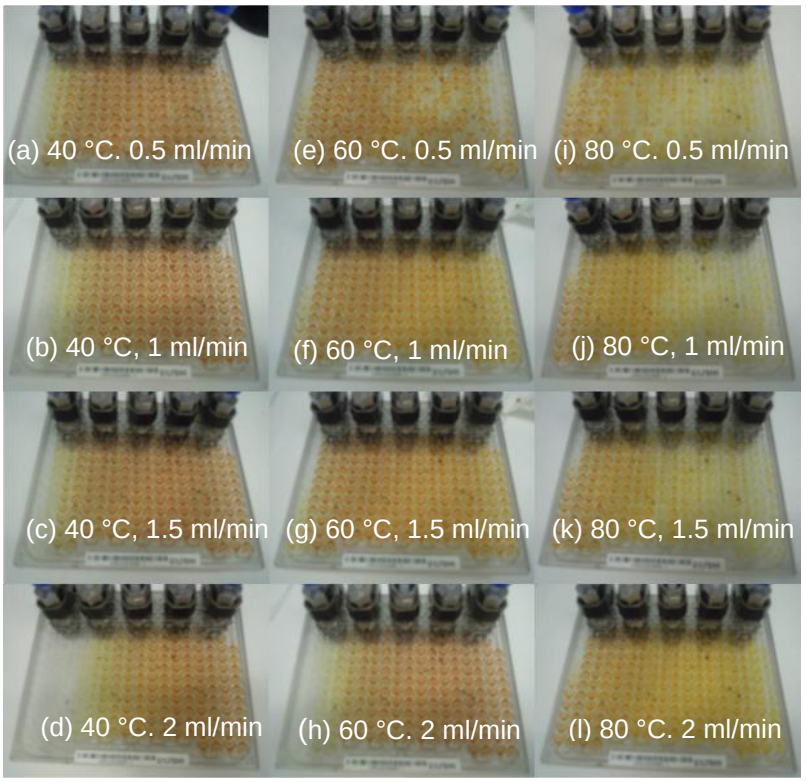


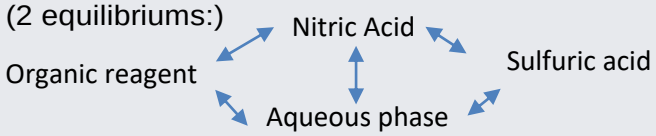
Figure 3: Aspect of FM during the reaction

Conclusion:

This shows a successful reaction setup. The two most important factors affecting the conversion of this reaction are temperature and stoichiometric ratio. Combining all the experimental data, using 4 equivalents of acetic anhydride at 80 °C would be good enough for a high conversion. The impact of higher initial concentrations can be tested. The residence time can be tested from 40s up to a few minutes, showing the interconnection of residence time and mixing. Variation of all parameters can be studied.

Tips & Tricks

This reaction is a demonstration reaction to illustrate the strong benefits from Nitration reaction in flow. In batch, these reactions are very synthetically useful but hard to control (thermal runway, oxidation...). Higher control benefits in flow conditions. There are many examples of successful industrial scale-up.
The ratio and mixing between reagents **is** critical. Both for the nitrating mixture (often sulfuric acid) and organic/aqueous phases (2 equilibriums:)



As unfavorable ratio can trigger runway, batch reactions are more prone to exothermic decomposition, and this translates in lower isomer selectivity
NB: The quench also is very exothermic and critical and benefits from a dilution prior to the quenching step.