THALESNano

Simple, Fast, and Safe Continuous Flow Nitrations with the IceCube™ Flow Reactor

INTRODUCTION

Nitration of aromatics is one of the oldest and industrially most important reactions. A reaction between an organic compound and a nitrating agent leads to the introduction of a nitro group onto a carbon, nitrogen or oxygen atom of that organic compound.

Nitro derivatives of aromatic compounds are used in a variety of basic and specialty chemicals that are employed in dyes, perfumes, pharmaceuticals, explosives, intermediates, colorants, and pesticides.

Almost 65% of APIs require at least one nitration step in the whole process.

NITRATION IN FLOW

In general, several types of nitrating agents are used for nitration. One third of the published literatures from the last 50 years report on nitrations of organic substrates with sulfuric acid and nitric acid as the nitrating agents[1].

Other types of nitration methods may also employ highly corrosive agents that together with the exothermic nature of such reactions require special instrumentations that can prevent both corrosion and enable ideal reaction conditions.

Continuous flow nitration using miniaturized devices is an excellent approach to avoid issues related to corrosion, heat transfer, mass transfer, homogeneity inside the reactor, and mixing.

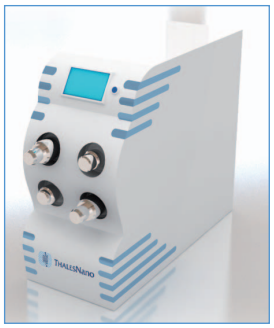
In this application note we share details of two nitration examples demonstrating the versatility of the IceCube flow reactor, dedicated to the safe running of exothermic reactions. The first reaction is the nitration of phenol, which was carried out at 10 °C providing 2-nitrophenol as the main product. In the second example, when toluene was nitrated with fuming nitric acid at -20 °C, precooling of the starting material was required before mixing and reacting them to form 2-nitrotoluene.

Ref: 1. Beilstein J. Org. Chem. **2014**, *10, 405–424.*

INSTRUMENTATION

The **IceCube™** reactor is made up of 4 modules: the Ozone Module, Pump Module, Reactor Module, and the Control Unit. The modules can be configured separately to match the application you wish to perform.

Reactor Module is a highly versatile reactor capable of controlling even extremely exothermic reactions safely and simply. Composed of two reactor zones with Peltier heating/cooling, and a reaction line made of Teflon for wide chemical compatibility. Difficult or dangerous reactions such as nitration, lithiation, azide generation or ozonolysis may now be performed and quenched immediately without the need for isolation of dangerous intermediates. Main reactor zone temperature range: -70-80°C, secondary reactor zone temperature range: -30-80°C.



Pump Module is made up of 2 rotary piston pumps, which have good chemical compatibility. The pumps are connected to two pressure sensors and 3-way valves, which control the path of reactant or solvent through the reactor. Flow rate: 0.2-4 mL/min. Max pressure: 6 bar

Ozone Module gives you a safe and efficient way of generating ozone from oxygen. The ozone/oxygen amount is precisely controlled through the built-in mass flow controller. The system can also be used as a powerful and compact stand alone ozonizer. Oxygen flow rate: 10-100 mL/min. O_3/O_2 v/v%: 14% at 20 mL/min oxygen flow rate.

Control Module is a small touch screen, which provides full control over all the attached modules. Reaction parameters can be easily set and monitored over time. The provided software has predefined processes for different applications, such as for ozonolysis, and it is also possible to design your own configuration.

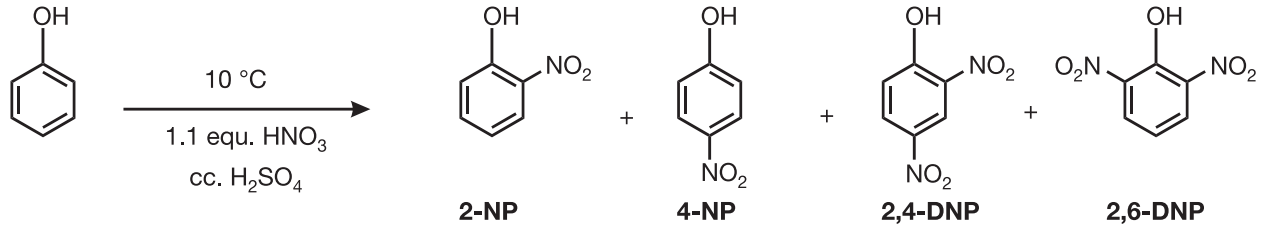
NITRATION OF TOLUENE IN FLOW

General Experimental Protocol

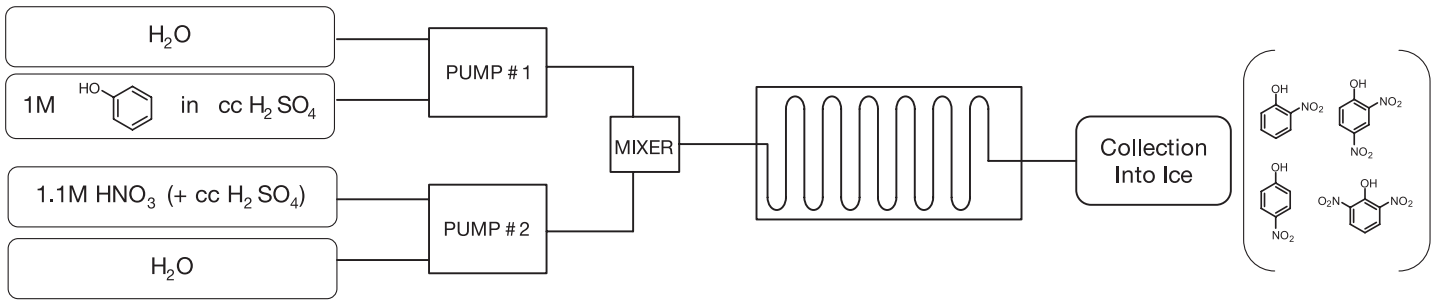
The nitrating mixture and the sulfuric acid solution of the phenol (1 M) were pumped into a PTFE T-piece by the system's inert rotary piston pumps. The combined reagent and reactant streamlines were then introduced into the IceCube flow reactor's first reactor zone, where the reactor plate was filled with a 2 mL 1/8" PTFE tube. As a last step, the nitrated compounds were collected onto ice. Scheme 1. represents the IceCube as it was set up for the nitration reaction, and Table 1 summarizes the reaction conditions with the results included.

CONCLUSION

The excellent chemical resistivity of the IceCube flow reactor system allowed the nitration of phenol in a continuous manner in minutes that together with the reactor's automated peltier cooling unit made sure that the heat generated was adequately dissipated during the course of such a highly exhothermic reaction. The temperature of the reaction was kept to a constant 10 °C. The integrated 3 way valves in each of the pumps enabled both safe and quick methods to flush out the residual acidic mixture from the system with water that made the system available for other types of exothermic flow reactions in minutes.



Reaction 1. Nitration of phenol in the IceCube flow reactor



Scheme 1. Reaction setup of the IceCube flow reactor for the nitration of phenol

	Flow rate (mL/min)		Reactor				Selectivity (%)			
Entry	Pump #1	Pump #2	Volume	Residence time	Temperature	Conversion (%)	2-NP	4-NP	2,4-DNP	2,6-DNP
1	0.2	0.2	2 mL (1/8")	5 min	10 °C	84	59.5	26.2	8.3	3.6
2	1	1	2 mL (1/8")	1 min	10 °C	84	60.7	23.8	10.7	4.8

Table 1. Experimental reaction conditions and results

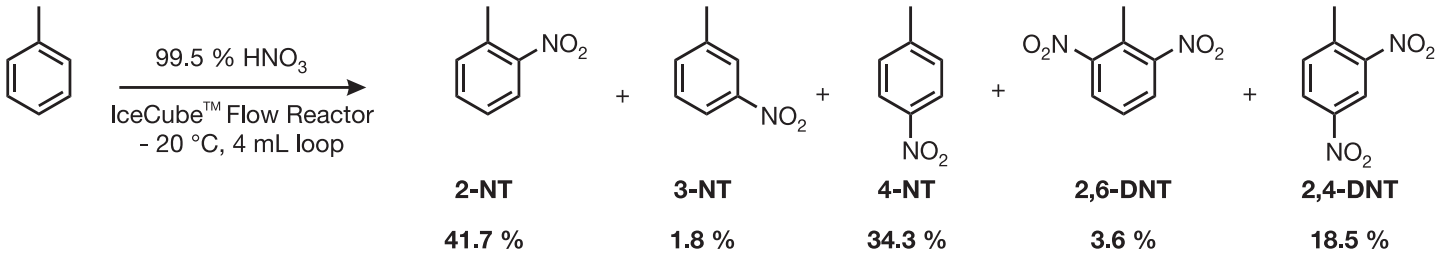
NITRATION OF TOLUENE IN FLOW

General Experimental Protocol

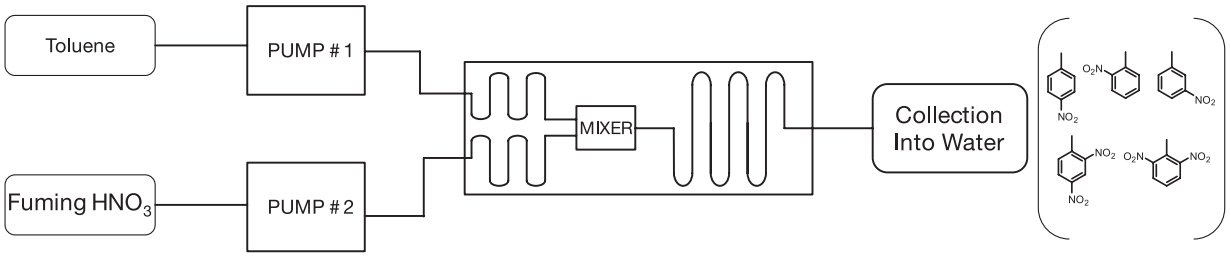
Fuming nitric acid and toluene were delivered into the first reaction zone of the IceCube flow reactor by the system's inert rotary piston pumps. Both materials were pumped through 2 ml precooling sections before they were combined by a PTFE T-piece. The combined reaction streams passed through a 4 mL PTFE reactor loop, in which the nitration was conducted at a constant -20 °C. Finally, the nitrated compunds were collected into water. Scheme 2 represents the IceCube as it was set up for the reaction, and Table 2 summarizes the reaction conditions with the results included.

CONCLUSION

Just as in the previous nitration example, the IceCube Flow reactor enabled safe and facile nitration of the toluene with fuming nitric acid. The automatic cooling system of the unit kept the reactor at the set -20 °C constantly, despite the several hundred kcal/mol reaction heat that was released during the course of the reaction.



Reaction 2. Nitration of toluene in the the IceCube Flow Reactor



Scheme 2. Reaction setup of the IceCube flow reactor for the nitration of toluene

	Flow rate (mL/min)		Acid equivalency	Precooling Volume (mL)			Reactor			Selectivity (%)				
Entry	Pump #1	Pump #2		Toluene	Nitric Acid	Temperature	Volume	Residence time	Temperature	2-NT	3-NT	4-NT	2,6-DNT	2,4-DNT
1	2	1	1.26	2	2	-20°C	4 mL	80 sec	-20 °C	41.7	1.8	34.3	3.6	18.5
2	2.8	1	0.9	2	2	-20°C	4 mL	63 sec	-20 °C	*GC-MS results did not indicate differences between Entry 1. and 2. results*				

Table 2. Experimental reaction conditions and results

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