Safe and Fast Ozonolysis Using the IceCube™ Flow Reactor

INTRODUCTION

Ozonolysis is a fundamentally important oxidation reaction, which has never been fully adopted due to the safety concerns with performing the process. Its main importance stems from the fact that you can selectively oxidize double or triple bonds to form hydroxyl groups, aldehydes, or carboxylic acids in the presence of other oxidizable groups (Figure 1). Other conventional oxidative methods are not so selective, are slower to react, require addition of water or need purification to eliminate side products leading to lower yields or need the use of metal catalysts. Compared to other methodologies, ozonolysis is considered as a greener way of oxidation. Ozonolysis has been used frequently in major drug syntheses such as (+)-Artemisinin, Indolizidine 251F, *and D,L*-Camptothecin and with finechemical syntheses such as *L*-Isoxazolylalanine and Prostaglandin endoperoxides.

FLOW OZONOLYSIS

In order to overcome the difficulties associated with ozonolysis, such as dangerous workup of the potentially explosive ozonide, use of low temperature, and complicated setting up of ozonizer equipment, ThalesNano has developed the IceCube™ flow reactor. The system is dedicated to performing ozonolysis and low temperature reactions. The IceCube™ reactor is safer and more efficient than standard batch equipment due to the small reactor volume and precise temperature control. The reactor design of the IceCube™ flow reactor allows chemists to carry out the formation and reductive or oxidative cleavage of the secondary ozonide in one instrument.

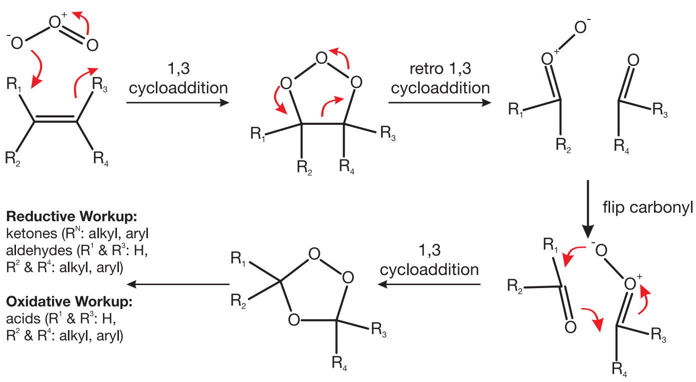
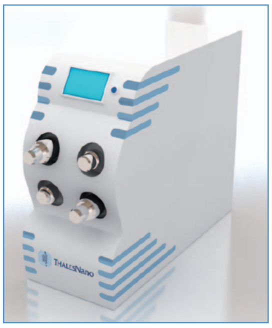


Figure 1. Mechanism of ozonolysis reaction

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. Maximum reaction pressure: 3 bar.

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.

GENERAL PROCEDURE

The Ozone Module™ generates ozone via a continuous flow of oxygen gas from a cylinder. The ozone is mixed with a continuous stream of precooled starting material in the Reactor Module. The liquid flow feed is supplied by one of the chemical resistant rotary piston pumps of the Pump Module. The gas/liquid mixture is then passed through a cooled reaction zone, where the ozonide formation takes place. After passing through the main reactor zone, the ozonide is mixed with the quenching reagent solution, supplied by the second rotary piston pump of the Pump Module. Immediate quenching is performed in a secondary reaction zone of the Reactor Module before eluting into a collection vial. All the reaction conditions, such as flow rates of the starting material and the quenching agent, the reaction temperature, and ozone amount were previously set on the Control Unit.

THE OZONOLYSIS OF INDOLE, STYRENE, AND EUGENOL

A DCM solution of the starting material was introduced into the main reaction zone of the IceCube™ flow reactor by one of the rotary piston pumps. The temperature of the reactor plate was kept at -10°C, and -20°C in case of the eugenol. The flow rate of the ozone/oxygen mixture was set to 50 mL/min providing 14 v/v % ozone. The gas and liquid lines were combined using a PTFE foam mixer before entering into a 4 mL teflon reactor loop. DMS was used as a quenching agent in a 0.2 M DCM solution. The DMS was introduced into the secondary reaction zone through the second rotary piston pump of the Pump Module. The biphasic mixture from the main reactor zone was combined with the quenching solution through a PTFE T-piece and was then fed into the PTFE loop of the secondary reactor zone. The temperature of the second reactor plate, where the quenching process was conducted, was kept at -10°C except for the eugenol example, which was -20°C. Analysis of the collected samples revealed the quantitative conversion of the indole, styrene, and eugenol. In every experiment high selectivity was achieved. Table 1. summarizes the used reaction conditions together with the results, while Figure 2. shows the schematics of the set up used during the reactions.

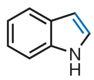
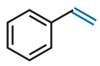
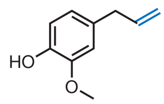
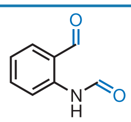
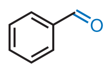
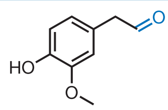
Entry	1	2	3
Starting Material *reaction media: DCM*			
Concentration *of the Starting Material*	0.1 M	0.2 M	0.1 M
Concentration *of the Quench Solution /Dimethyl Sulfide in DCM/*	0.2 M	0.2 M	0.1 M
Pump flow rate [mL/min] *of the Starting Material*	0.5	1.0	1.0
Pump flow rate [mL/min] *of the Quench Solution*	0.6	1.0	1.0
O_2 flow rate [mL/min]	50	100	50
Reactor Volume	4 mL	4 mL	4 mL
Reactant Precooling	No	Yes (2 mL)	Yes (2 mL)
Reactor Temperature	-10°C	-10°C	-20°C
Quench Reactor Volume	3 mL	2 mL	2 mL
Quenching Temperature	-10°C	-10°C	-20°C
Product			
Conversion	100%	100%	98%
Selectivity	94%	92%	83%
Calculated Yield	94%	92%	81%

Table 1. Examples of ozonolysis with the IceCube flow reactor

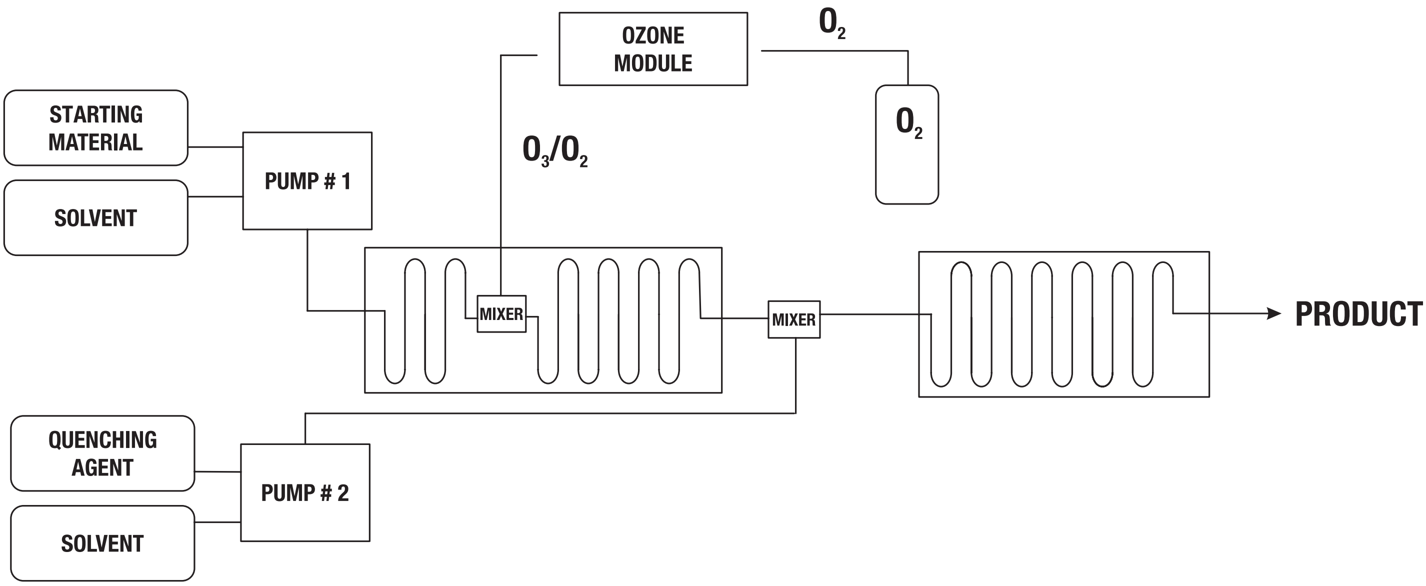


Figure 2. Reaction setup of the IceCube flow reactor for ozonolysis

CONCLUSION

The Ozone Module enabled a quick and reliable O_3 generation that, together with the reactor's excellent heat transfer capability and instantaneous ozonide quenching features, allowed very quick, highly safe, and selective ozonolysis reactions even at temperatures of 10-20°C below zero.

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