



Project:

O-Cube™ Product White Paper

„Ozonolysis Reinvented”

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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. 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 yields¹. 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. However, the use of ozonolysis as a technique is performed less and less due to the safety concerns associated with performing the reaction.

Ozone is an unstable gas and can be explosive. The ozonide formed by reacting ozone with a double bond can be unstable and can decompose to explosive effect. Chemists have sought to avoid ozonolysis by utilizing the reagent osmium tetroxide, but this in itself is highly toxic. The apparatus used to perform ozonolysis today does not embolden today's chemist to perform the technique. Typically, ozonolysis is performed by attaching an oxygen cylinder to a commercial ozonizer. Ozone itself is usually generated in a laboratory by passing dry air or oxygen through two electrodes connected to an alternating current source of several thousand volts². The ozone is then passed through a solvent trap and into a cooled, stirred solution of the olefin. Once the solution has turned blue, indicating that the olefin has been consumed, a reductive or oxidative reagent is then added to the formed ozonide to produce the desired product. Ozonolysis is typically carried out at low temperatures, between -25 and -78 to control the temperature of this exothermic reaction, to increase the solubility of ozone, and to diminish vapour tension to keep solvent evaporation low.

There are several major drawbacks to this method:

- The apparatus is a collection of parts and not a purpose designed equipment.
- Each parameter has to be monitored continuously increasing the strain on resources.
- The temperature is difficult to control in batch and this difficulty increases with increased reaction size. If the reaction temperature is not closely observed a run away reaction may occur leading to explosive decomposition of the ozonide.

The use of microreactors to perform ozonolysis may eliminate many of these concerns. The advantages of using flow reactors are well known³. These include preciser control of

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temperature, reaction stoichiometry, mixing, and reaction mixture residence time. Our previous success with continuous flow hydrogenation⁴ led us to apply our knowledge in flow chemistry reactors to ozonolysis and help make this technique more prevalent in industry.

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O-Cube™ Overview



- Temperature range: -25°C to room temperature
- Pressure Range: The system operates at atmospheric pressure. Higher pressures decomposes the ozone and reduces ozone concentration.
- The liquid flow rate range of the system is 0.1-2 mL/min. Syringe pumps are utilized to avoid any of the issues caused by HPLC pump check valve failures.
- The ozone concentration produced is 15 wt-% from an oxygen cylinder. There is also an option to generate oxygen gas using an oxygen generator.
- The oxygen gas flow rate is set to 20 cm³/min.
- All the reaction parts are made from PTFE and ceramic to give high chemical resistance and to maintain the stability of the ozone.
- Scale: Capable of producing from 10mg-10g of product per day. Higher amounts may be generated by leaving the O-Cube™ to generate product continuously over longer periods of time.

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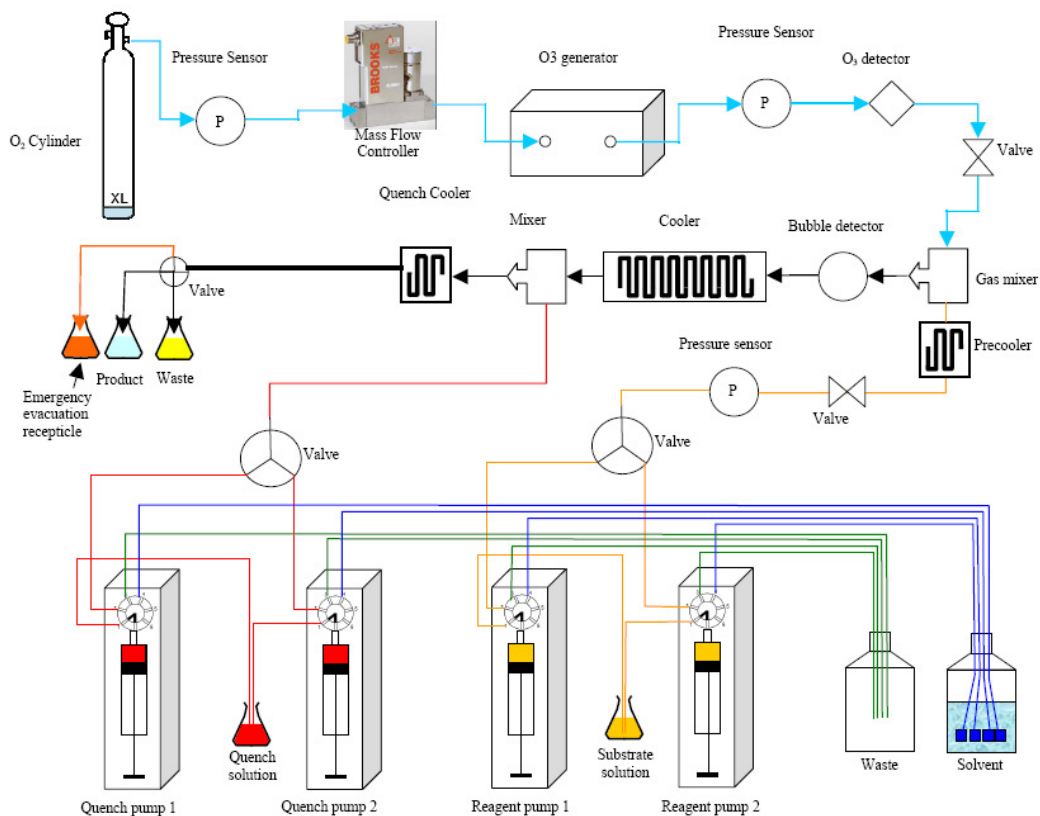
- High-quality, robust design, easy to handle and operate
- A number of safety features including:
 - Ozone detector for ozone leak detection
 - Temperature limit shutdown
 - Pressure limit shutdown
 - An uninterruptable power supply (UPS) which maintains control of the O-Cube™ and shuts the system down in the event of a power cut.
- Full system Touch Screen control and monitoring

Method Description

The O-Cube™ generates ozone via a continuous flow of oxygen gas, from a cylinder, through an ozonizer. The flow of oxygen is controlled using a mass flow controller up to a maximum flow rate of 20mL/min. The ozone produced is quantified using an internal analyzer and passed through a polytetra-fluoroethylene (PTFE) frit with a porosity of 20µm where it mixes with a continuous stream of substrate. The flow of substrate is controlled using two syringe pumps with PTFE heads. The stream of substrate is pumped through a precooler before mixing with the ozone. Once the ozone is mixed with the flow of substrate the gas/liquid mixture is pumped into a cooler, which may be cooled down to a temperature of -20°C. The cooler is a PTFE tube wrapped around a refrigerator unit. The volume of the tubing is 10 cm³. After passing through the cooler, the formed ozonide mixes with quench reagent solution, supplied by two separate syringe pumps. The quenching is performed in a secondary cooler before eluting into a collection vial. A schematic of the system is displayed in Scheme 1. The flow system has many advantages over its batch counterparts. Performing ozonolysis is safer because the ozonide is formed and reacted continuously. The volume of ozonide formed is no larger than 10 cm³. Temperature control of the formation on ozonide or the subsequent quenching of the ozonide is easier to control. The flow rate can be varied to accurately

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control the residence time of the ozonide in the reaction line. As with all flow reactors, the required amount in milligrams or grams can be produced by leaving the system running to produce the required quantity.



Scheme 1: Schematic of the O-Cube™ System

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Advantages

Safety – Only a small amount of the ozonide is generated and then quenched continuously. The temperature of the reaction is therefore more easily controlled and monitored.

Reaction Control – The accurate control of temperature in the O-Cube™, coupled with a uniform temperature and mixing across the reaction zone means that the same experiment can be repeatedly performed at the same reaction parameters giving the same result.

Selectivity – The residence time of the substrate in the reactor can be very precisely controlled using flow rate down to the second. This allows users to target one of a multiple choice of products, by restricting the time of the substrate spent reacting.

Quick Optimization - Temperature and flow rate may be changed “on the fly” for quick reaction optimization. Versatile - Other low temperature reactions such as lithiation, diazotization, Grignard, and Wittig reactions may also be run on the reactor.

Ease of Use - The software that controls the reactor is incredibly easy to use. The software has a timer function where the reaction may be set up and left to react without the need for user monitoring.

Convenience – The small footprint and the simplicity means the O-Cube™ may be used in any lab and by any chemist opening up ozonolysis to a new level of chemist.

Data export – All parameters of the experiment such as reactor temperature, quench temperature, pressure, gas flow, and flow rate may be monitored during the reaction and

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the data exported using a USB stick at the end of the experiment.

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Reaction Examples

The following is a series of validation reactions to test the applicability and the capacity of the system and reacted on a 100mg scale.

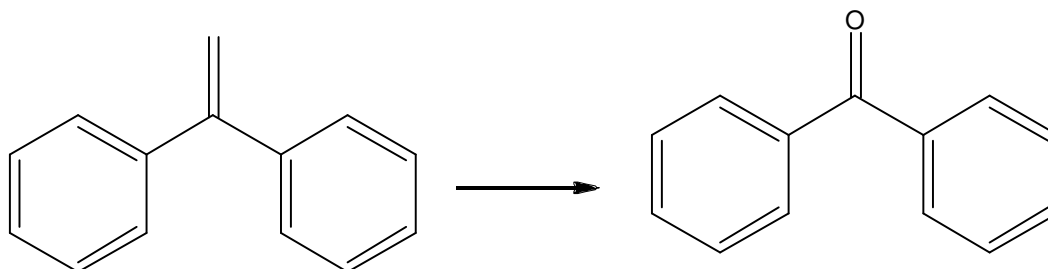
Materials and General Methods

GC-MS Analysis of the Product Mixture was conducted using a 6850 Gas Chromatograph for GC/MSD System and 5975C VL MSD Mass Spectrometer fitted with a HP1 capillary column (15 m, i.d. 0.25 mm, and film thickness 0.25 μ m) and EI detector. A split flow of 49.8 mL/min and Helium gas was used. Temperature gradient: 50 °C for 3 min; 50 to 200 °C at 7.5 °C min⁻¹.

LC-MS analysis of the product mixture was performed using an Agilent 1100 liquid chromatograph fitted with a LiChroCART® 30-4 Purospher® STAR RP-18 endcapped 3 μ m column and DAD detector coupled with a Waters micromass ZQ MS detector. Eluent gradient: Eluent „B” steadily increased from 0% to 100% during 4 minutes, then from 4 to 6 minutes 100% eluent „B”, and from 6 to 6.10 minutes eluent „B” steadily decreased to 0%. The flow rate was 1.5 mL/min. (Eluent „A” contained: Water:Acetonitrile:Buffer = 46.5:2.5:1, Eluent „B” contained: Water:Acetonitrile:Buffer = 9:40:1. The buffer contained: Water:Ammonium hydroxide solution (25%):Formic Acid=20:2.2:1)

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Ozonolysis of diphenyl-ethylene



M=180 g/mol

M=182 g/mol

Optimal conditions:

Reagent concentration= 0.1M

Quench concentration= 0.1M

Temperature: RT

Solvent: Ethyl-acetate

Reagent flow rate: 0.5mL/min

Quench flow rate: 0.5mL/min

Quench: Diphenyl-sulfide

Gas flow: 10mL/min

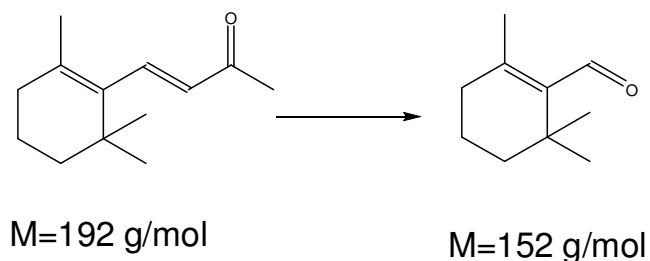
Ozone (wt-%): 13-15%

Conversion:>99%

Selectivity:>99%

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Ozonolysis of beta-ionone



Optimal conditions:

Reagent concentration= 0.1M

Quench concentration= 0.3M

Temperature: RT

Solvent: ethanol

Reagent flow rate: 1 mL/min

Quench flow rate: 1 mL/min

Quench: Thiourea

Gas flow: 20mL/min

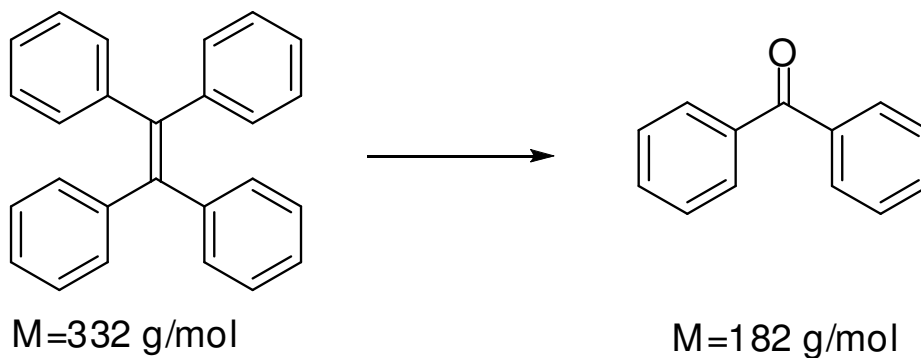
Ozone (wt-%): 13-15%

Conversion:>70%

Selectivity:>99%

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Ozonolysis of tetraphenyl ethylene



Optimal conditions:

Reagent concentration= 0.01M

Temperature: RT

Solvent: 1,2-DCE

Substrate flow rate: 1mL/min

Quench: NaBH₄

Gas flow rate: 20mL/min

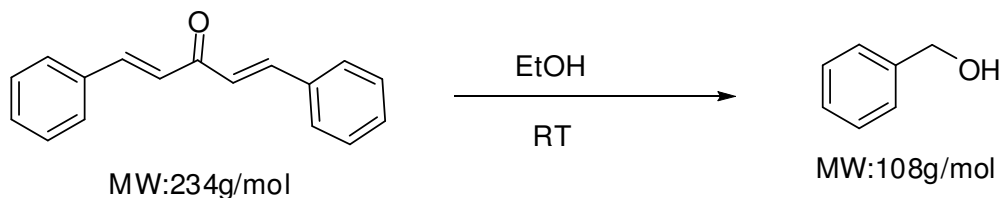
Ozone (wt-%): 7%

Conversion:>99%

Selectivity:>99%

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Ozonolysis of diphenyl pentadienone



Optimal conditions:

Reagent concentration= 0.05M

Temperature: RT

Solvent: Ethanol

Substrate flow rate: 0.5mL/min

Quench: NaBH₄ in ethanol

Gas flow rate: 20mL/min

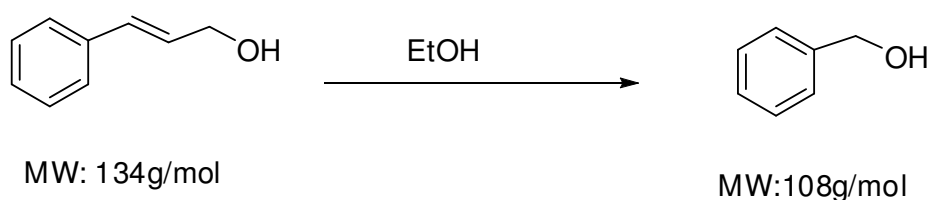
Ozone (wt-%): 8%

Conversion:>99%

Selectivity:>99%

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Ozonolysis of cinnamic alcohol



Optimal conditions:

Reagent concentration= 0.05M

Temperature: RT

Solvent: Ethanol

Reagent flow: 0.5-1mL/min

Quench: NaBH₄ in ethanol

Gas flow rate: 20mL/min

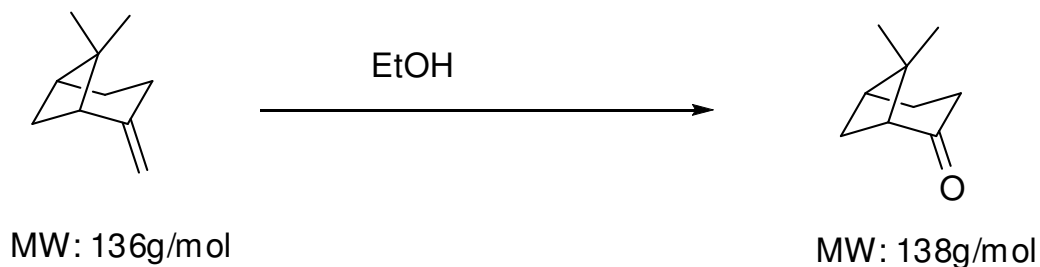
Ozone (wt-%): 7%

Conversion:>99%

Selectivity:>99%

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Ozonolysis of beta-Pinene:



Optimal conditions:

Reagent concentration= 0.05M

Temperature: RT

Solvent: Ethanol

Reagent flow rate: 0.5mL/min

Quench: NaBH₄ in ethanol (pumping ozonide into quench batch)

Gas flow rate: 20mL/min

Ozone (wt-%): 7%

Conversion:>99%

Selectivity:>90%

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Summary

The O-Cube™ is able to oxidise a variety of different compounds to form alcohols, ketones, aldehydes and epoxides easily and safely. The system controls all parameters and has a timer function for true walk away functionality. With O-Cube™, chemists can now start to use ozonolysis to its full potential making reaction schemes shorter and creating more diverse compounds.

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