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Process intensification of ozonolysis reactions using dedicated microstructured reactors

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Ozonolysis reactions are generally high-yielding, highly selective, and sustainable processes, especially when performed in green solvents. However, ozonolysis is underutilized in organic synthesis and chemical manufacture due to the safety concerns associated with handling ozone (O₃) gas and the highly reactive ozonide intermediate. In this article, the development of ozonolysis reactions within a dedicated microreactor platform suitable for gas-liquid transformations is described. The optimization of the reaction conditions for the ozonolysis of cyclohexene to hexanedial, and thioanisole to methyl phenyl sulfoxide is presented. Cyclohexene is transformed to hexanedial in 94% yield at 0 °C within 1.7 seconds. In a similar fashion, the ozonolysis of thioanisole was achieved in 99% yield at 0 °C within <1 second. A 3D printed heat flow calorimeter was used to measure the heat of reaction for the ozonolysis of thioanisole, giving a value of -165 ± 4 kJ/mol. A 3 hour long run achieved a throughput of 1.77 g/h for methyl phenyl sulfoxide, which corresponds to a space time yield of 1.84 kg L⁻¹ h⁻¹ for this intensified process.

A classical approach used for the oxidation of organic substrates is through ozonolysis with ozone (O₃) gas.¹ O₃ can be generated in situ by directly passing air or pure oxygen through two electrodes connected to an alternating current source of several thousand volts. By using pure oxygen, ozone generators can produce up to 18% of O₃ in O₂. The cost of O₃ is relatively inexpensive when derived from pure O₂. Ozone is used to cleave alkenes, alkynes or aromatics giving a variety of derivatives, with the particular outcome mainly depending on the workup conditions.² In general, ozonolysis reactions are highly selective and provide high product yields. Typically, only oxygen is formed as a stoichiometric by-product, which makes ozonolysis reactions very green.³

The main limitation of ozonolysis reactions are the

associated safety concerns, particularly at industrial scales. O₃ is a highly reactive and poisonous gas with a characteristic pungent odor. The main safety concern when operating under batch conditions is the accumulation of ozone within the liquid phase. Furthermore, ozonolysis reactions can involve the formation of a highly reactive ozonide intermediate, which may undergo sudden exothermic decomposition. Thus, low temperatures, typically between -78 to 0 °C, are required, with the lower temperatures being very costly and energy intensive at large scale.⁴ Ozonolysis reactions are performed in organic solvents under an oxygen-rich atmosphere, therefore there is a potential risk of fire or explosion. At large scales, ozonolysis reactions are usually performed in batch reactors with elaborate safety measures, including the use of cryogenic temperatures, low substrate concentrations and dilution with inert gas to ensure that there is less than 10% O₂ content in the headspace.⁵

Continuous flow technologies have been demonstrated to overcome many of the limitations associated with batch reactors.⁶ Gas-liquid reactions that were deemed to be too dangerous or difficult to handle in batch are possible due to the high surface-to-volume ratio within microreactors.⁷ The characteristics of microreactors enable excellent thermal management, short mixing times and rapid mass transfer. In particular, studies have demonstrated that the risk of uncontrolled explosion using higher concentrations of O₂ gas can be minimized through the utilization of microreactors due to the relatively low internal volumes and reactor pressure resistance.⁸ Microreactor technologies can also be reliably scaled-up through a smart dimensioning approach to manufacture production level quantities.⁹

Jensen and co-workers reported the first study of ozonolysis reactions within a microreactor system (50 μL volume) achieving throughputs of between 0.009 and 0.016 mmol/min, depending on the substrate used. In this study they investigated the oxidation of phosphites, amines and olefins.¹⁰ Since then, ozonolysis reactions have been performed using simple T-mixers,¹¹ capillary reactors,^{12,13} tube-in-tube reactors,¹⁴ microstructured reactors,¹⁵ loop reactors,¹⁶ spray reactors,¹⁷ and packed SiO₂ columns without the use of a

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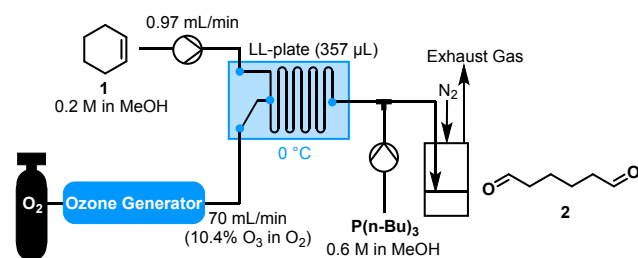
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solvent.¹⁸ In general, the main limitation of many of the aforementioned examples is that the achieved throughput is relatively low and issues related to mass and heat transfer remain. Herein, we discuss the development of highly intensified ozonolysis reactions within a dedicated and scalable microreactor platform that addresses mass and heat transfer issues effectively and provides high throughputs.

We commenced our investigations with the ozonolysis of cyclohexene (**1**) to hexanedial (**2**). The batch ozonolysis of various cyclohexene derivatives has already been extensively studied.^{4,19} A schematic of the flow system used in our study is shown in Scheme 1 (see also Fig. S4). The continuous flow system utilized a Modular MicroReaction System (MMRS) equipped with a FlowPlate Lab (357 μL volume, nominal channel width 0.2 mm, Hastelloy C22), manufactured by Ehrfeld Mikrotechnik.²⁰ A LL mixing plate was used, since a LL mixing structure has been demonstrated to be optimal for biphasic gas-liquid reactions.²¹ An ozone module from ThalesNano was utilized for the in situ generation of the ozone from pure O_2 ,²² and for the controlled introduction of the gas feed into the reactor plate. Gas flow rates are given in the unit of mL/min, where $T = 25\text{ }^\circ\text{C}$ and $P = 1.0\text{ bar}$, and were measured and controlled using a mass flow controller contained in the ozone module. The liquid feeds (substrate and reducing agent) were introduced by syringe pumps (Syrris Asia). After the mixing of the substrate feed and gas feed within the plate, an annular flow regime was always observed under the flow rates used in this study, which was expected based on the high gas flow rate and relatively low liquid flow rate. The quench feed was either introduced via a T-piece, or using an inlet within the reactor plate to further decrease the residence time of the ozonolysis. The temperature within the system was controlled by a thermostat (Huber, Ministat 240).



Scheme 1. Continuous-flow setup for the ozonolysis of cyclohexene.

Initially, a feed solution of 0.05 M of cyclohexene (**1**) in MeOH at a flow rate of 1.83 mL/min and a gas flow rate of 20 mL/min (17% O_3 in O_2 , 1 eq. O_3) were used. The reaction was quenched by introducing a feed of tributylphosphine in MeOH.²³ This initial experiment resulted in close to quantitative conversion and a hexanedial (**2**) yield of 89.6% within 4.8 s residence time (Table 1, entry 1).²⁴ Using MeOH as a solvent rather than chlorinated solvents clearly improves the greenness of this process.²⁵ Furthermore, the use of MeOH enhances the safety of the reaction, because it has a different reaction pathway than when performed using dichloromethane as solvent (see Fig. S2 & S3). When MeOH is

used as solvent then no secondary ozonide is formed, but a hydroperoxo-hemiacetal, which has a lower thermal decomposition potential to the secondary ozonide.²⁶ When using MeOH as solvent it was important to ensure that mixing and quenching is performed rapidly and in the correct manner to avoid reaction with MeOH.

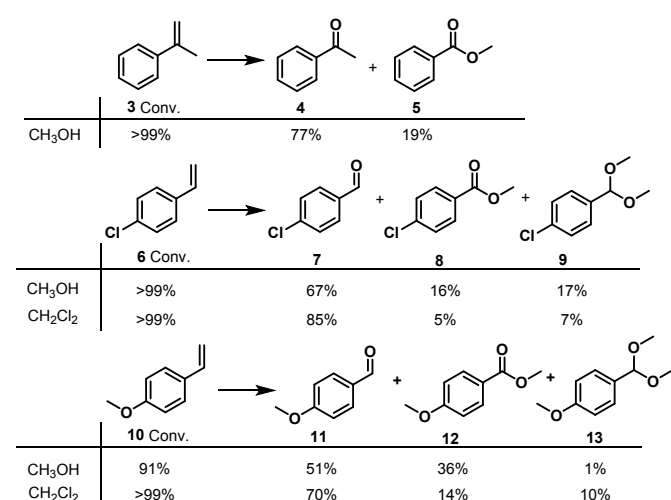
Subsequently, we investigated the influence of increasing the cyclohexene (**1**) concentration to 0.2 M. The liquid flow rate was set to 0.972 mL/min and the gas flow rate was also increased to 70 mL/min (10% O_3 in O_2). These conditions provided full substrate **1** conversion and a 94.1% yield of the desired hexanedial (**2**) within 1.7 s residence time (entry 2). Higher substrate concentrations ($>0.2\text{ M}$) were not feasible as the maximum flow rate of the ozone module is 100 mL/min, providing 8.5% O_3 in O_2 (see also Fig. S1). The residence time was further decreased by using an inlet (Q3) within the reactor plate for the introduction of the quench solution. Decreasing the residence time for the ozonolysis reaction to less than 0.1 s decreased the conversion of substrate to 89.3% (entry 3). Subsequently, the influence of temperature was investigated (entry 4), with $-20\text{ }^\circ\text{C}$ affording product **2** in 91.7% yield and a similar amount of side products formed compared to experiments at $0\text{ }^\circ\text{C}$. By using 0.7 equivalents of reducing agent, a drop in the yield of **2** and a higher amount of an unidentifiable side product was observed due to an increase in reaction with MeOH. 1.3 and 3.1 equivalents of reducing agent were also investigated (entries 6 and 7), with higher equivalents resulting in a slight decrease in the yield of **2**. Switching to sodium metabisulfite as the quenching reagent resulted in a significant drop in the yield of **2** (entry 8), which demonstrates that the reaction outcome is very dependent on the particular reducing agent employed.²⁷ In summary, the optimal operating conditions for the preparation of hexanedial (**2**) from cyclohexene (**1**) were determined to be: **1** (0.2 M in MeOH) with a pump flow rate of 0.972 mL/min, $0\text{ }^\circ\text{C}$, 1 equiv. O_3 (70 mL/min, 10% O_3 in O_2) and with a residence time of 1.7 s, and 1 equiv. of tributylphosphine (0.6 M in MeOH) with a flow rate of 0.326 mL/min.

After showing the ability to perform ozonolysis with cyclohexene (**1**), the optimal conditions were applied to other olefins (Scheme 2). The ozonolysis of 2-phenylpropene (**3**) provided full conversion, 77% yield of acetophenone (**4**) and 19% yield of methyl benzoate (**5**) as side product. The ozonolysis of *p*-chlorostyrene (**6**) also provided full conversion and afforded a mixture of products with the desired aldehyde **7** in 67% yield, and the ester **8** and hemiacetal **9** side products in 16% and 17% yield respectively. There was slightly lower conversion achieved when using *p*-methoxystyrene (**10**) as substrate, affording the aldehyde **11** in 51% yield and the ester **12** in 36% yield. The side products were formed because the reaction with MeOH occurred faster than the reduction reaction. The results using MeOH as solvent were then compared to CH_2Cl_2 for *p*-chlorostyrene (**6**) and *p*-methoxystyrene (**10**). Gratifyingly, this resulted in full conversion and increased formation of the desired aldehyde products in both cases, as MeOH was only introduced as part of the quench feed.

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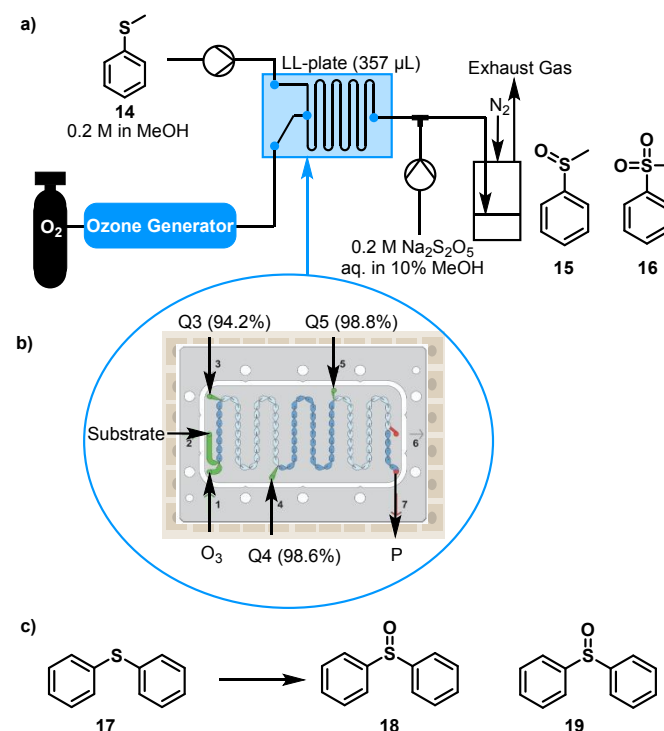
Table 1. Results from the ozonolysis of cyclohexene (**1**). The conditions used (unless otherwise stated) are shown in Scheme 1, with the exception of entry 1. Q stands for quench, which was performed at inlet 3 within the mixing plate. ^aBased on GC-FID area%

	Substrate 1 conc. [mol/L]	Temperature [°C]	Equiv. Ozone	Equiv. Quench	Reactor Plate	Residence Time [s]	1 Conversion [%] ^a	2 Yield [%] ^a
1	0.048	0	1.03	1.03	LL	4.8	97.2	89.6
2	0.203	0	1.01	1.00	LL	1.7	99.4	94.1
3	0.203	0	1.00	1.00	LL (Q at 3)	<0.1	89.3	79.0
4	0.203	-20	1.00	1.00	LL	1.7	99.8	91.7
5	0.203	0	1.01	0.69	LL	1.7	99.4	76.8
6	0.203	0	1.01	1.29	LL	1.7	99.9	93.2
7	0.203	0	1.01	3.06	LL	1.7	99.9	88.9
8	0.203	0	1.02	Na ₂ S ₂ O ₅ (1.00)	LL	1.9	99.3	18.2

**Scheme 2.** Ozonolysis of further olefin substrates. Conditions: 0.2 M substrate in solvent, substrate feed flow rate = 750 μ L/min, gas flow rate = 50 mL/min (12% O₃ in O₂), 0.2 M Na₂S₂O₅ aq. (10% MeOH), quench feed flow rate = 800 μ L/min. Conversion and yields determined by GC-FID in area%.

Another important reaction using ozone gas is the oxidation of sulfides to their corresponding sulfoxides.²⁸ With the knowledge from cyclohexene in hand, we then investigated the ozonolysis of thioanisole (**14**) to methyl phenyl sulfoxide (**15**) (Scheme 3). One challenge associated with the oxidation of thioanisole is avoiding the overoxidation to methyl phenyl sulfone (**16**). The reaction was studied in a similar manner as for cyclohexene. The reaction was quenched either in a T-piece or within the reactor plate by a 0.2 M Na₂S₂O₅ aqueous solution (10% MeOH). Sulfoxide **15** was formed in 98.5% yield at 0 °C with 1 equiv. of ozone within the LL process plate (Table 2, entry 1). The residence time was

further decreased by using different inlets within the reactor plate for the introduction of the quench solution (entries 2-4 and Scheme 3b).

**Scheme 3.** a) Flow setup for the ozonolysis of thioanisole (**15**); b) The structure of the LL process plate is depicted; c) the conditions (Table 2, entry 9) were then applied to the oxidation of diphenyl sulfide (**17**) to the diphenyl sulfoxide (**18**) and diphenyl sulfone (**19**). Q3, Q4 and Q5 stands for the different inlets used to introduce the quench solution in Table 2, entries 2-4.

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Table 2. Process intensification for the ozonolysis of thioanisole (**14**) and diphenylsulfide (**17**) (entry 9). Conditions: 0.2 M substrate in MeOH, substrate feed flow rate = 750 $\mu\text{L}/\text{min}$, gas flow rate = 50 mL/min, quench feed flow rate = 800 $\mu\text{L}/\text{min}$. Q stands for quench. ^aBased on GC-FID area%. ^bDiphenyl sulfide (**17**). ^cDiphenyl sulfoxide (**18**). ^dDiphenyl sulfone (**19**).

Entry	Temperature [°C]	Equiv. Ozone	Reactor	Residence Time [s]	14 Conversion [%] ^a	15 Yield [%] ^a	16 Yield [%] ^a
1	0	1.04	LL	1.7	99.8	98.5	1.3
2	0	1.03	LL (Q at 5)	0.33	99.6	98.8	0.8
3	0	1.03	LL (Q at 4)	0.19	99.7	98.6	0.7
4	0	1.01	LL (Q at 3)	0.04	94.6	94.2	0.4
5	-30	1.08	LL	2.3	98.0	94.2	1.5
6	-15	1.07	LL	2.2	98.6	94.2	1.4
7	0	1.06	LL	2.0	99.0	95.8	1.3
8	15	1.05	LL	1.9	99.3	96.2	1.5
9 ^b	0	1.02	LL	1.7	99.8 ^b	98.0 ^c	1.8 ^d

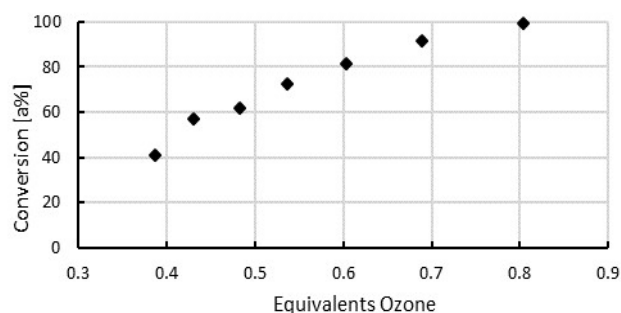


Figure 1. Influence of the ozone equivalents on the conversion of **4**. Based on the general conditions given in Table 2, entry 1 the liquid flow rate was varied to achieve the desired ozone equivalents.

A residence time of 0.19 seconds was sufficient to provide quantitative conversion of thioanisole (**14**) (entry 3). Decreasing the residence time to 0.04 seconds resulted in a drop in conversion and desired product **15** yield (entry 4). These results clearly demonstrate that the ozonolysis is very fast and mostly likely a mass transfer limited process. Subsequently, we investigated the influence of temperature between -30 and 15 °C (entries 5-8). Higher temperatures afforded a slight increase in the conversion of **14** and product **15** yield. A longer residence time and higher temperature also resulted in a slight increase in formation of methyl phenyl sulfone (**16**).

There are high concentrations of oxygen/organic vapor, creating a large inventory of potentially flammable mixture within the collection vessel headspace.^{8a} The flash point is typically defined as the lowest temperature at which the vapor will form a combustible mixture with air. Operation at 0 °C is preferred, since the temperature should be kept below the

flash point of a water-methanol mixture in pure oxygen (between 5 and 12 °C) to prevent explosions in the collection flask, where the gas-liquid separation is performed and there is a large volume of gas present, and make the process as safe as possible.²⁹ The likelihood of explosions was further minimizing by flushing the collection vessel with N₂ to ensure operation below the limiting oxygen concentration (LOC) value (for MeOH 7.6 vol% O₂ at 1 bar).³⁰ The LOC value is defined as the minimum partial pressure of oxygen that supports a combustible mixture; below this level combustion will not occur.

The equivalents of ozone necessary were also investigated, see Fig. 1. Full conversion could be achieved with 0.8 equivalents of ozone (0.8 molecules ozone for 1 molecule thioanisole). Full conversion, even when using substoichiometric amounts of ozone, could possibly be explained by the radical reaction mechanism proposed.³¹ The ozonide intermediate can react with a second sulfide if it is not quenched fast enough. The further reduction of the equivalents of ozone showed a clear drop in conversion. The successful application of the optimized conditions for thioanisole oxidation to diphenyl sulfide (**17**) as substrate afforded 98% yield of diphenyl sulfoxide (**18**) (entry 9). The ozone utilization towards the desired reaction (defined as moles of desired product formed/mol of O₃ fed) is close to 1 or higher in all of the examples presented herein, thus demonstrating the highly efficient use of O₃.³²

As batch experiments for highly exothermic reactions can be very dangerous if heat accumulation is not kept low, continuous calorimetry can enhance safety by providing efficient heat transfer and precise control over the dosing of feeds. Nobis and Roberge reported typical reaction enthalpies between -200 to -400 kJ/mol for ozonolysis reactions.¹⁶ These reaction enthalpies were measured in an RC-1 heat

flow batch calorimeter. Prior to performing a long run, we were interested in measuring the heat of reaction for the ozonolysis of thioanisole (**14**). A modular continuous flow isothermal heat flow calorimeter with Peltier elements was used. The full details of the calorimeter design has recently been reported elsewhere.³² We performed two experiments within the flow calorimeter, using 1 and 1.4 equiv. ozone. The experiments were performed at 25 °C, since this temperature does not require careful pre-cooling of the feeds prior to entering the calorimeter. The flow calorimeter contains 3 separate microstructured 3D-printed zones: pre-heating, reaction 1 and reaction 2 (further details can be found in the ESI Section 5). For both experiments, all the heat was released within the reaction 1 segment, clearly showing that a 110 μL reactor volume to be sufficient for the oxidation of thioanisole (0.55 s residence time). The calorimetry experiments resulted in a measured heat of reaction (ΔH) of -165 ± 4 kJ/mol,³⁴ which corresponds to a calculated adiabatic temperature rise of 16.0 °C.³⁵

To show the stability of the identified optimal operating conditions, an experiment for the ozonolysis of thioanisole (**14**) was performed over 3 hours operation time (substrate feed: 1.18 mL/min, 0.2 M thioanisole and 70 mL/min 10.2% O₃ in O₂ at 0 °C in the LL plate; quench: 0.94 mL/min, 0.21 M Na₂S₂O₅). After work-up, this process afforded methyl phenyl sulfoxide (**15**) in 89% isolated yield (99.5% purity). Using this setup, a throughput of 1.77 g/h of **15** was obtained, corresponding to a space time yield of 1.84 kg L⁻¹ h⁻¹, including the quench reactor volume. As a comparison, the productivity in our previous study for the flow ozonolysis of thioanisole (**14**) achieved a throughput of 0.313 g/h, which corresponded to a space time yield of 0.0782 kg L⁻¹ h⁻¹.¹³ Transfer to a larger scale can be achieved by applying “smart dimensioning” by increasing the channel dimensions and a plate designed to be geometrically equivalent to the lab version for the necessary gas–liquid mixing function.^{20,21} When running at higher flow rates, it ensures the same mixing efficiency and similar heat exchange capacities as for the smaller plate reactor.

In conclusion, high-yielding and highly selective ozonolysis reactions have been developed within a dedicated microreactor system ensuring exquisite control over mass and heat transfer for these very fast gas–liquid transformations. All of the ozonolysis reactions investigated occur within very short reaction times (<2 s), utilize temperatures that are readily accessible for larger scale applications (0 °C), and enable safe handling by avoiding a large inventory of ozone gas and highly unstable ozonide intermediates due to the very small reactor volume (<357 μL). Furthermore, a 3D printed isothermal heat flow calorimeter in continuous flow mode was used to measure the heat of reaction for the ozonolysis of thioanisole. This result demonstrates that a reaction which would be otherwise difficult to investigate in a batch calorimeter can be studied by using a microstructured flow calorimeter. The microreactor technology utilized facilitates potential scale-up through the application of a smart dimensioning strategy. Research in our laboratories will further investigate scale-up to larger scale continuous reactors.

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Conflicts of interest

There are no conflicts to declare.

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