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Continuous Flow Ozonolysis in a Laboratory Scale Reactor

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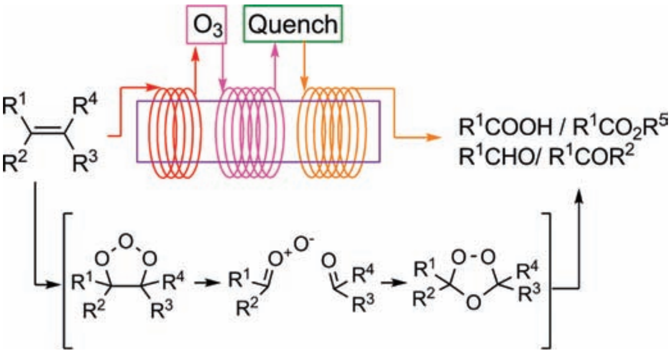
ABSTRACT



Several important types of ozonolysis reactions have been performed in a continuous flow device that is able to perform both the ozonolysis and quenching steps in flow mode. This technique allows safe and scalable ozonolysis reactions to be performed on a laboratory scale.

Ozonolysis has been extensively studied for several decades after the apparently first report by Schönbein in 1855.[1] Considered as a clean and efficient way of introducing oxygen-containing groups (alcohols, aldehydes, ketones, or acids) by oxidative cleavage of C−C double bonds, ozonolysis has become a common tool for synthetic chemists in academic and industrial research laboratories.[2] From the mechanistic standpoint, ozonolysis reactions represent a sequence of 1,3-cylcoaddition−reversion steps according to the most widely accepted Criegee mechanism for liquid-phase ozonolysis.[3]

In the classical view of the reaction, the 1,3-cycloaddition of an ozone molecule to a C−C double bond leads to the initial formation of a 1,2,3-trioxolane ring (primary ozonide, "molozonide"). Subsequent ring cleavage results in a highly reactive dipolar carbonyl oxide intermediate and an aldehyde or a ketone, which then recombine to provide a 1,2,4-trioxolane (secondary ozonide). Upon oxidative or reductive cleavage (quenching) the latter heterocycle can then be converted into aldehydes, ketones, alcohols, or acids.[2,3]

Although an intrinsically environmentally benign and atom-efficient oxidation process compared to analogous metal-mediated transformations, a major concern in ozonolysis chemistry is safety,[4] since the formed ozonides (and peroxides) are unstable and potentially explosive. Furthermore, the subsequent quenching step to produce the final products is generally an exothermic process, requiring efficient temperature control. Arguably, given the hazard

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[1] Schönbein., C. F. *J. Prakt. Chem.* **1855**, *66*, 282.

[2] (a) Bailey, P. S. *Chem. Rev.* **1958**, *58*, 925–1010. (b) Bailey, P. S. *Ozonolysis in Organic Chemistry*; Academic Press: New York, 1978; Vol. 1. (c) Odinokov, V. N.; Tolstikov, G. A. *Russ. Chem. Rev.* **1981**, *50*, 636–656. (d) Bailey, P. S. *Ozonolysis in Organic Chemistry*; Academic Press: New York, 1982; Vol. 2. (e) Bunnelle, W. H. *Chem. Rev.* **1991**, *91*, 335–362. (f) Ishmuratov, G. Y.; Kharisov, R. Y.; Odinokov, V. N.; Tolstikov, G. A. *Russ. Chem. Rev.* **1995**, *64*, 541–568. (g) Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990–3001. (h) Zvereva, T. I.; Kasradze, O. B.; Kazakova, O. B.; Kukovinets, O. S. *Russ. J. Org. Chem.* **2010**, *46*, 1431–1451.

[3] (a) Murray, R. W. *Acc. Chem. Res.* **1968**, *1*, 313–320. (b) Criegee, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 745–751. (c) Kuczkowski, R. L. *Acc. Chem. Res.* **1983**, *16*, 42–47. (d) Kuczkowski, R. L. *Chem. Soc. Rev.* **1992**, *21*, 79–83. (e) Schank, K. *Helv. Chim. Acta* **2004**, *87*, 2074–2083.

[4] Kula, J. *Chem. Health Saf.* **1999**, *6*, 21–22.

10.1021/ol102984h

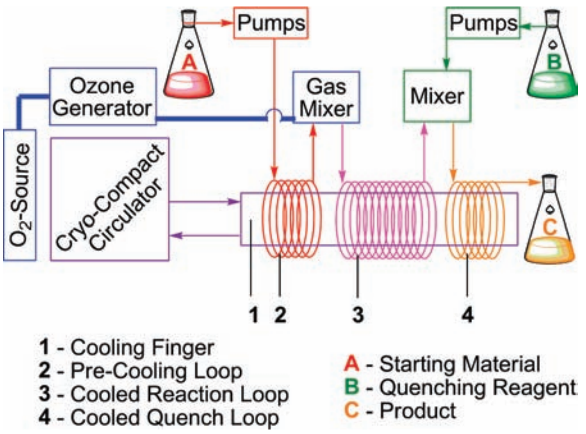
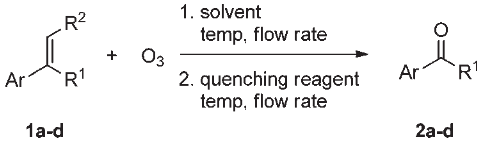
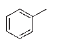
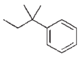
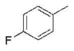
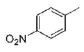
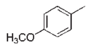


Figure 1. Simplified schematic view of the O-Cube reactor.

Table 1. Flow Ozonolysis of Selected Styrenes



Ar	R^1	R^2	step 1	step 2	product (%)[a]
		H	MeOH 25 °C 1 mL/min	$NaBH_4$/ MeOH 25 °C 0.7 mL/min	90
	CH_3	H	Me_2CO 0 °C 1mL/min	5% H_2O/Me_2CO 10 °C 0.7 mL/min	91
	H	H	Me_2CO 25 °C 1 mL/min	5% H_2O/ Me_2CO 25 °C 0.7 mL/min	84
	H	CH_3	Me_2CO 10 °C 1 mL/min	5% H_2O/ Me_2CO 15 °C 0.7 mL/min	72

[a] Isolated yield.

of forming potentially explosive intermediates and considering the toxicity of O_3 itself, traditional batch ozonolyis reactions have little prospect of becoming fully integrated into the arsenal of synthetically useful (and safe) laboratory procedures.[5]

Recently, continuous-flow processing and microreactor technology have gained increased attention as valuable alternatives to batch protocols.[6,7] Dedicated flow reactors have been employed successfully in the past for performing highly exothermic reactions or in cases where hazardous (explosive, toxic) reagents or intermediates are involved.[6,7] The small reactor volumes and high heat transfer rates characteristic of these devices can mitigate the risks normally experienced in a batch process.[6,7] Therefore, the concept of continuous flow ozonolysis appears to be highly attractive. In recent years, several dedicated flow/microreactor devices have been described in the literature, able to effectively perform ozonolysis reactions for specific applications.[8−12] Nonetheless, the development of a general purpose laboratory scale continuous flow ozonolysis system is still in its infancy.

Herein we report a variety of ozonolysis reactions performed in a dedicated commercially available flow device. The flow ozonolysis reactor (O-Cube) is a compact benchtop instrument suitable for atmospheric pressure ozonolysis from −25 °C to room temperature at 0.2−2.0 mL/min flow rates, capable of producing up to 10 g of material per day (Figure 1).[13]

The instrument uses an O_2 gas cylinder to supply an inbuilt O_3 generator with a continuous flow of O_2 at a maximum flow rate of 20 mL/min. The generated O_3 is quantified in an internal analyzer and passed through a polytetrafluoroethylene (PTFE) frit to mix with a continuous stream of dissolved substrate (**A**). The substrate flow is maintained by two syringe pumps equipped with PTFE heads. The stream of substrate is continuously cooled before and after being mixed with O_3. The cooled reaction loop is a 4 mL (reaction volume) 1 mm i.d. PTFE tube wrapped around a refrigeration unit. After passing through the reaction loop, the formed ozonide mixes with the quench reagent solution (**B**), supplied by two further syringe pumps. Finally, the formed product is eluted into a collection vial (*CAUTION! As the formed ozonides and/or peroxides are potentially explosive, the reaction mixture has to be subjected to further workup only after NEGATIVE test with peroxide test strips*).

In order to investigate the scope and potential of this technology we have explored various common ozonolysis

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(5) Despite this fact, industrially important ozonolysis processes have been carried out on considerable scale. For details, see: Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Ripin, D. H. B. *Chem. Rev.* **2006**, *106*, 2943–2989 and citations therein.

(6) Selected reviews on microreactor technology, see: (a) Fukuyama, T.; Rahman, M. T.; Sato, M.; Ryu, I. *Synlett* **2008**, 151–163. (b) Wiles, C.; Watts, P. *Eur. J. Org. Chem.* **2008**, 1655–1671. (c) Geyer, K.; Gustafsson, T.; Seeberger, P. H. *Synlett* **2009**, 2382–2391. (d) Hartman, R. L.; Jensen, K. F. *Lab Chip* **2009**, *9*, 2495–2507. (e) McMullen, J. P.; Jensen, K. F. *Annu. Rev. Anal. Chem.* **2010**, *3*, 19–42.

(7) (a) Wirth, T., Ed. *Microreactors in Organic Synthesis*; Wiley-VCH: Weinheim, 2008. (b) Hessel, V., Schouten, J. C., Renken, A., Wang, Y., Yoshida, Y.-i., Eds. *Handbook of Micro Reactors*; Wiley-VCH: Weinheim, 2009. (c) Yoshida, J.-i. *Flash Chemistry−Fast Organic Synthesis in Microsystems*; Wiley-VCH; Weinheim, 2008. (d) Luis, S. V., Garcia-Verdugo, E., Eds. *Chemical Reactions and Processes under Flow Conditions*; Royal Society of Chemistry: Cambridge, 2010.

(8) Wada, Y.; Schmidt, M. A.; Jensen, K. F. *Ind. Eng. Chem. Res.* **2006**, *45*, 8036–8042.

(9) (a) Steinfeldt, N.; Abdallah, R.; Dingerdissen, U.; Jähnisch, K. *Org. Process Res. Dev.* **2007**, *11*, 1025–1031. (b) Hübner, S.; Bentrup, U.; Budde, U.; Lovis, K.; Dietrich, T.; Freitag, A.; Küpper, L.; Jähnisch, K. *Org. Process Res. Dev.* **2009**, *13*, 952–960. (c) Steinfeldt, N.; Bentrup, U.; Jähnisch, K. *Ind. Eng. Chem. Res.* **2010**, *49*, 72–80.

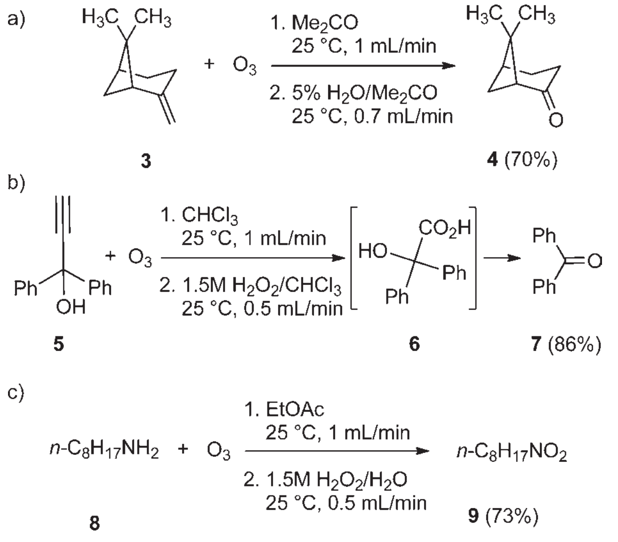
(10) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596–1598.

(11) (a) Pelletier, M. J.; Fabilli, M. L.; Moon, B. *Appl. Spectrosc.* **2007**, *61*, 1107–1115. (b) Pflieger, M.; Monod, A.; Wortham, H. *Atmos. Environ.* **2009**, *43*, 5597–5603. (c) Pflieger, M.; Goriaux, M.; Temime-Roussel, B.; Gligorovski, S.; Monod, A.; Wortham, H. *Atmos. Chem. Phys.* **2009**, *9*, 2215–2225. (d) Gomes, A. C.; Nunes, J. C.; Simões, R. M. S. *J. Hazard. Mat.* **2010**, *178*, 57–65.

(12) Allian, A. D.; Richter, S. M.; Kallemeyn, J. M.; Robbins, T. A.; Kishore, V. *Org. Process Res. Dev.* **2011**, *15*, 91−97.

(13) For more details, see: http://www.thalesnano.com/products/o-cube.

Scheme 1. Flow Ozonolysis of Various Substrates



processes in combination with either oxidative or reductive quenching/workup steps. We initially examined the continuous flow ozonolysis of several styrenes (**1a**−**d**) as model substrates.[14]

In a single pass through the continuous flow reactor, solutions of **1a**−**d** readily afforded the corresponding aldehydes/ketones **2a**−**d** in 72−90% isolated yield (Table 1), comparable to the published batch ozonolysis results.[14] Typically, a 0.05 M stock solution of the corresponding styrene **1a**−**d** in methanol (MeOH) or acetone (Me_2CO) as solvent was passed through the ozonolysis device at 0−25 °C using 5% ozone concentration (1.5 equiv) and a 0.7−1.0 mL/min flow rate.

The degree of conversion can easily be determined by monitoring the composition of the reaction mixture after being exposed to the ozonolysis conditions by HPLC or GC−MS analysis. For all of the examples covered in this manuscript, full conversion of the starting material was achieved. Adjusting the proper settings on the instrument (O_3 concentration, temperature, and flow rate) allowed the facile optimization of the reaction conditions in these and related transformations (see Table S1 in the Supporting Information for details). Using the above-described conditions, typically 100−215 mg of product could be produced within a 40 min run.

A major advantage of the flow-through concept concerns the handling of the excess ozone and ozonides (or peroxides) present in the reaction mixture. In the current system, the quenching step is performed immediately after the substrate has left the ozonolysis coil, destroying any excess O_3 and transforming the ozonide intermediates into the corresponding product. In the case of aldehydes/ketones **2a**−**d** (Table 1) the only remaining workup that is required is an extraction followed by solvent evaporation, producing the desired products in >95% purity (^{1}H NMR, HPLC/GC−MS) and high yields.

Similarly, 4-methoxybenzaldehyde **2d**, after isolation from the initial ozonolysis step **1d** → **2d**, could be further oxidized to 4-methoxybenzoic acid with 1.5 equiv of O_3 in $CHCl_3$ followed by an oxidative quench. In addition, when using methanol as solvent, the ozonolysis of 4-fluoro-α-methylstyrene (**1b**) resulted in the selective formation of methyl 4-fluorobenzoate in 72% isolated yield (see Supporting Information for details).

In another example, we were able to convert β-pinene (**3**) into nopinone (**4**) in a single continuous-flow experiment (Scheme 1a). Whereas the groups of Brown and Dumas performed batch ozonolysis experiments at −78 °C in order to obtain the nopinone structure after a Me_2S quench (83% and 85% yield),[15] using the O-Cube reactor allowed us to perform the oxidative process under ambient conditions (25 °C) at a 1 mL/min flow rate to obtain nopinone (**4**) in 100% conversion and 70% isolated yield after chromatograhpy, using H_2O/acetone as quenching reagent (Scheme 1a). In addition to olefinic double bonds, the ozonolysis of the terminal C−C triple bond in 1,1-diphenylprop-2-yn-1-ol **5** (Scheme 1b) was also investigated. In our hands, the ozonolysis of propynol **5** in $CHCl_3$ did not lead to the expected glycolic acid **6**[16] but to diphenylketone **7** in 86% yield. The observed result can be rationalized by the presence of ozone in the reaction mixture, creating an oxidizing environment, able to rapidly decarboxylate the in situ formed glycolic acid, thereby forming diphenylketone **7** as observed previously by Hurd and Christ for similar substrates.[17]

In another application of the continuous flow ozonolysis concept, we attempted the oxidative transformation of octan-1-amine **8** (Scheme 1c) into the corresponding nitroalkane **10**. Previous work by Bachman and Strawn has confirmed that primary amines of type **8** can be subjected to ozonolysis under batch conditions to provide nitroalkanes,[18] and the Jensen group has reported the oxidation **8** → **9** with O_3 in a multichannel microreactor.[8] Adopting operating conditions similar to those used during olefin ozonlysis, a 0.05 M EtOAc solution of octan-1-amine **8** was subjected to flow ozonolysis in the O-Cube at room temperature. Applying a 10% ozone concentration (~3 equiv), complete consumption of the starting material was experienced, providing 1-nitrooctane **9** in 73% yield after a single pass through the instrument within 40 min. The oxidation of thioanisole (**10**) appeared to be a somewhat more demanding process, as it has been found that aliphatic/aromatic or aromatic/aromatic thioethers tend to react relatively slowly or not at all with ozone (thioesters).[19] While the formation of the sulfoxide proceeds relatively

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[14] (a) Wacek, A. V.; Eppinger, H. O. *Chem. Ber.* **1940**, *73*, 644–651. (b) Keaveney, W. P.; Berger, M. G.; Pappas, J. J. *J. Org. Chem.* **1967**, *32*, 1537–1542. (c) Schiaffo, C. E.; Dussault, P. H. *J. Org. Chem.* **2008**, *73*, 4688–4690.

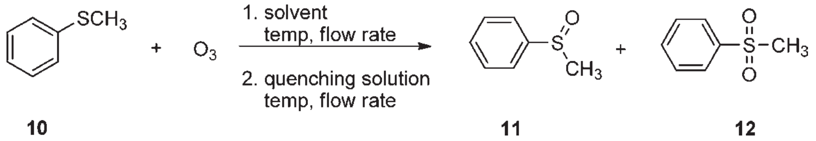
[15] (a) Brown, H. C.; Weissman, S. A.; Perumal, P. T.; Dhokte, U. P. *J. Org. Chem.* **1990**, *55*, 1217–1223. (b) Dumas, F.; Alencar, K.; Mahuteau, J.; Barbero, M. J. L.; Miet, C.; Gerrd, F.; Vasconcellos, L. A. A.; Costa, P. R. R. *Tetrahedron: Asymmetry* **1997**, *8*, 579–583.

[16] (a) Cannon, J. G.; Darko, L. L. *J. Org. Chem.* **1964**, *29*, 3419–3420. (b) DeMore, W. B.; Lin., C.-L. *J. Org. Chem.* **1973**, *38*, 985–989.

[17] Hurd., C. D.; Christ, R. E. *J. Org. Chem.* **1936**, *1*, 141–145.

[18] Bachman, G. B.; Strawn, K. G. *J. Org. Chem.* **1968**, *33*, 313–315.

Table 2. Selectivities in the Flow Ozonolysis of Thioanisole (**11**)



								conv % (GC−MS)		
entry	O_3 (equiv)	solvent	step 1 (mL/min)	temp (°C)	quenching solution	step 2 (mL/min)	temp (°C)	10	11	12
1	1	MeOH	1	25	0.1 M $NaBH_4$/MeOH	0.7	25	0	99[a]	0
2	2	Me_2CO	0.5	25	0.05 M $NaIO_4/H_2O$	1	25	0	82	18
3	2	Me_2CO	0.5	10	1 M H_2O_2/H_2O	1	15	0	57	43
4	2	Me_2CO	1	5	3 M H_2O_2/H_2O	1	10	0	22	78
5	2	Me_2CO	1	5	5 M H_2O_2/H_2O	1	10	0	12	88
6	2	MeOH	1	−10	5 M H_2O_2/MeOH	1	0	32	0	68
7	2	MeOH	1	−20	5 M H_2O_2/MeOH	1	−10	14	0	86
8	4	MeOH	0.5	−20	5 M H_2O_2/MeOH	0.5	−10	0	0	99[b]

[a] Isolated yield 84%. [b] Isolated yield 87%.

slowly, the further oxidation step to the sulfone is known to be even more sluggish.[19] Therefore, we investigated the oxidation behavior of thioanisole (**10**) with ozone under flow conditions. Initially, a 0.05 M solution of thioanisole (**10**) in methanol was processed at 25 °C and 1 mL/min flow rate applying 5% O_3 (1.0 equiv). Reductive quenching with 0.1 M $NaBH_4$ in MeOH at 25 °C followed by extractive workup provided sulfoxide **11** in 84% isolated product yield (Table 2, entry 1).

In order to access sulfone **12** the reductive quench was replaced by an oxidative one (Table 2, entryies 2−8). Using $NaIO_4$ as oxidative reagent at 25 °C and 2 equiv of O_3 in acetone, full conversion based on consumption of sulfide **10** was achieved at a 0.5 mL/min flow rate in the ozonolysis step. Analysis (GC−MS) of the obtained reaction mixture showed predominant formation of sulfoxide **11** accompanied by 18% of the desired sulfone **12** (Table 2, entry 2). Lower temperatures and higher flow rates, as well as changing the oxidative reagent to 5 M H_2O_2 in water as solvent led to an improved sulfoxide/sulfone product distribution (Table 2, entries 3−5) providing up to 88% selectivity for sulfone **12**. Ultimately, changing the reaction solvent to MeOH initially did not seem promising (Table 2, entry 6); however, after further optimization we were finally able to achieve quantitative conversion of thioanisole **10** into the desired sulfone **12**. Under the optimized conditions for full conversion (Table 2, entry 8) a preparative experiment provided 87% isolated yield of sulfone **12** after a simple workup.

In conclusion, a novel continuous flow laboratory scale ozonolysis instrument has been described. The flow ozonolysis of aromatic/aliphatic olefins and an alkyne as well as the oxidation of an amine into the corresponding nitro-compound and the selective oxidation of an aromatic thioether into the corresponding sulfoxide and sulfone have been conducted successfully. In all of these processes, the highly energetic ozonolysis and quenching reactions were performed safely in flow format with excellent temperature control, avoiding the inventory of the highly unstable ozonide intermediates. The application of this novel reactor for a range of more complex ozonolysis reactions is currently in progress in our laboratories.

Acknowledgment. This work was supported by a grant from the Christian Doppler Research Society (CDG). M.I. thanks the Higher Education Commission of Pakistan for a Ph.D. scholarship. We thank ThalesNano Nanotechnology Inc. (Budapest, Hungary) for the provision of the O-Cube ozonolysis reactor.

Supporting Information Available. Full experimental details and spectral data (NMR, MS) for all transformations and compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Horner, L.; Schaefer, H.; Ludwig., W. *Chem. Ber.* **1958**, *91*, 75–81.