Ozonolysis in Flow using the Vapourtec System

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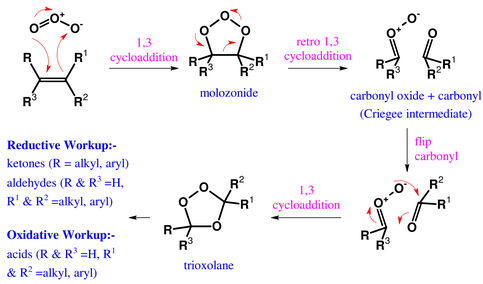
Introduction

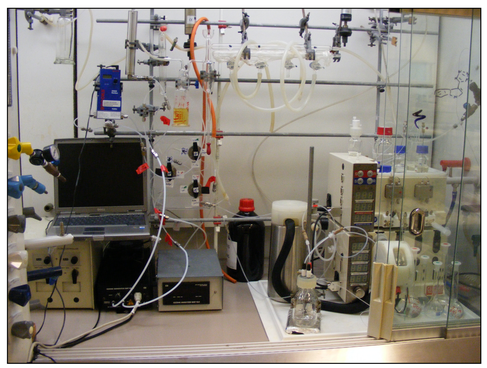
Ozone is an oxidant that has been used for decades in organic synthesis and in the purification/deodorisation of water.[1] Ozonolysis is the addition of ozone to a substance resulting initially in a primary ozonide (molozonide) which then usually rearranges to a more stable secondary ozonide (trioxolane) in the case of alkenes (Scheme 1).

Scheme 1

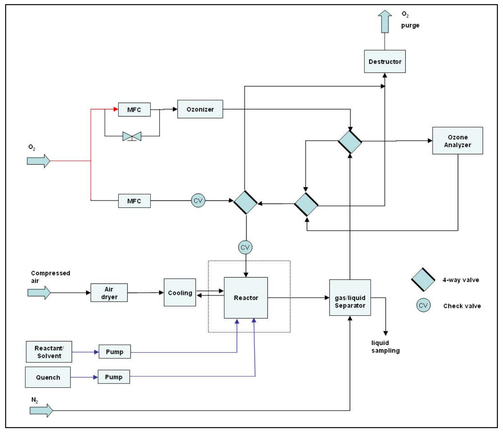


This transformation has great utility in synthesis both in a research and an industrial setting. The advantage of using ozone followed by reductive workup over other oxidants is the low cost and toxicity of the by-products i.e. DMSO from DMS, Ph_3PO from PPh_3 as compared with high oxidation level metallic oxidants e.g. Chromium. Some of the drawbacks of using ozone at scale are the high exotherms associated with the initial reaction of substrates with ozone. Also the intermediate ozonides are unstable (although some can be isolated at room temperature) and are an explosion risk due to the weak O-O single bond. Thus, the build up of these materials must be avoided. The use of continuous flow can alleviate both the exotherm problem and the build up of potentially explosive materials (if suitable reagents are used to quench them in flow).

Setup



The Vapourtec R4 system is a widely established piece of equipment in an industrial R & D setting and has many uses in liquid-liquid systems. Most R & D centres also have access to an ozoniser. The coupling of these relatively common pieces of equipment gives many advantages over a purpose built system; these are modularity, cost, versatility and simplicity.



Above is a schematic showing the apparatus used in this work. The Vapourtec R4 is connected to an ozoniser and ozone analyser. The Vapourtec cooled reactor module was used to attain the low temperatures required to control the exothermic reaction. Three four-way valves were used to enable the location of the ozone analyser to be "hot switched" from before to after the reactor module.

Chemistry

Initial studies were carried out using the aliphatic alkene 1-decene **1** and triethylphosphite as the reductive quench reagent (Scheme 2, Table 1).

Scheme 2

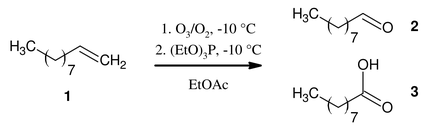


Table 1

Entry	Decene[1] (ml/min)	EtO_3P[1] (ml/min)	O_2/O_3[1] (ml/min)	Cartridge (ml)	Nonanal[2]	Nonanoic Acid[2]	Decene[2]
1	0.25 (1.0)	0.25 (1.5)	25 (2.4)	10	1.0	0.50	ND
2	0.50 (1.0)	0.50 (1.5)	25 (1.2)	10	1.0	0.40	0.2
3*	0.25 (1.0)	0.25 (1.5)	25 (1.2)	10	1.0	0.50	ND
4	0.25 (1.0)	0.25 (1.5)	25 (2.2)	2	1.0	0.50	ND
5	0.25 (1.0)	0.25 (1.5)	25 (1.5)	2	1.0	0.42	ND
6	0.25 (1.0)	0.25 (1.5)	25 (1.5)	0.07	1.0	0.34	ND

1. Equivalents shown in brackets; 2. GC ratios; * Decene 0.4 M, $(EtO)_3P$ 0.6 M.

Successful conversion of 1-decene to products with as little as 1.2 eq. of O_3 and a small reactor cartridge (volume = 0.07 ml) was achieved. Unfortunately the selectivity for the aldehyde was poor and after further studies it was found that the intermediate trioxolane was being inefficiently reduced to the desired aldehyde **2**. It was concluded that triethylphosphite was unable to reduce the ozonides cleanly within the short reaction times seen in the flow reactor.

Triphenylphosphine is a stronger reducing agent than triethylphosphite and it was able to furnish the desired nonanal with a good selectivity of >10:1 (Table 2).

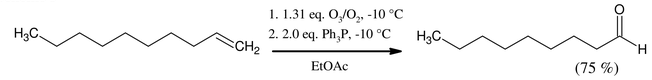
Table 2

Entry	Decene[1] (ml/min)	Ph_3P[1] (ml/min)	O_2/O_3[1] (ml/min)	Coil (ml)	Nonanal[2]	Nonanoic Acid[2]	Decene[2]
1	0.30 (1.0)	0.40 (2.0)	25 (1.50)	2	1.0	0.13	ND
2	0.36 (1.0)	0.48 (2.0)	25 (1.25)	2	1.0	0.04	ND
3	0.72 (1.0)	1.44 (2.5)	50 (1.25)	2	1.0	0.02	ND

All runs carried out at -10 °C. 1. Equivalents shown in brackets; 2. GC ratios referenced to nonanal.

A larger scale run was carried out at 13 mmol/hr and achieved a good yield of 75 % of this difficult to isolate aldehyde (Scheme 3).

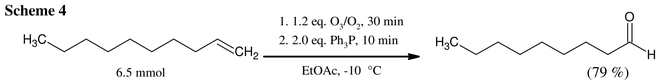
Scheme 3



Decene:	0.2 M in EtOAc (1.08 ml/min)
Ph_3P:	0.3 M in EtOAc (1.44 ml/min)
Ozone:	206 g/Nm^3 (66 ml/min)
O2 Pressure	1.299 +/- 0.005 bar abs.
Reaction Coil	2ml (-10 °C)
Throughput	1.8 g/hr (13.0 mmol/hr) 30 min run.

This result was compared to an equivalent batch experiment and was found to be comparable (Scheme 4).

Scheme 4



Other quench reagents were also evaluated these included DMS, thiodipropionic acid, Zn/AcOH and *N*-methylmorpholine-*N*-oxide, but none were as efficient as triphenylphosphine for a fully "in flow" process.

Conclusions

- An ozoniser and analyser were successfully interfaced with a Vapourtec R4 flow reactor in a highly configurable fashion.
- For 1-decene ozonolysis, several quench reagents were analysed and only triphenylphosphine was deemed efficient in non-participating solvents.
- A large scale flow run was compared to an equivalent batch run and found to be comparable at 13 mmol/hr.

Future work

- Broaden scope to include a fully reductive quench to furnish alcohols.
- The ozoniser is capable of generating ozone at levels over two orders of magnitude higher and therefore could be coupled with larger flow technology.
- Utilise the accuracy of ozone delivery and fast reaction/quench times possible to explore the selective ozonolysis of multifunctional substrates.

References

1. Bailey, P. S., Ozonation in Organic Chemistry, Vol 1. Olefinic Compounds, 1978; Vol 2. Nonolefinic Compounds, Academic Press, New York, 1982.

Acknowledgements

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