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Alkene ozonolysis in the academic lab

June 27, 2017

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The following information is offered as a guide based upon our experience with application of ozone for organic oxidations and hydroperoxide synthesis. Please send suggestions, requests, or corrections to pdussault1@unl.edu.

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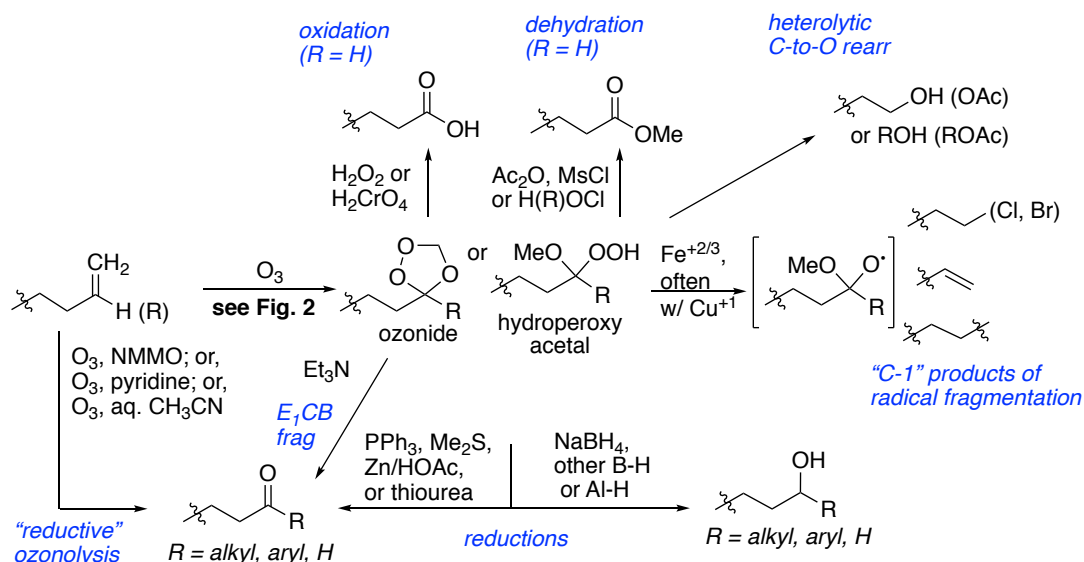
Reaction work-ups

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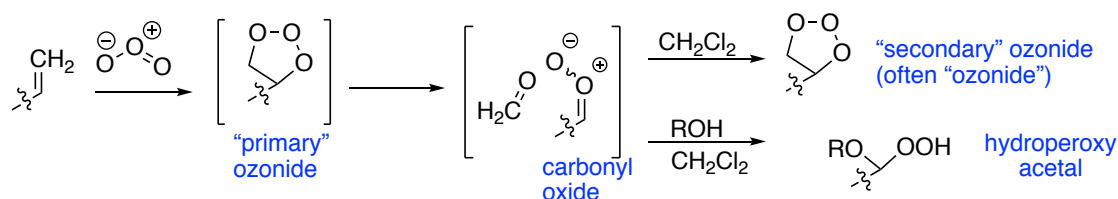
Acknowledgements:

Introduction and leading references

The following provides a brief introduction to the application of ozonolysis within academic labs. Ozonolysis remains among the most frequently used of methods for oxidative cleavage of alkenes. While best known as a means by which to introduce aldehydes and ketones, ozonolysis can also be used to generate other functional groups. An overview of some of the most common ozonolysis transformations illustrated in Figure 1; the reader is directed to a recent review for more information and leading references.¹ A number of useful technical documents are available online.²

Figure 1. Overview of typical applications of ozonolysis (see ref. 1 for more detail)**Overview of alkene ozonolysis:**

Ozone reacts with most alkenes to form short-lived 1,2,3-trioxolanes, aka "primary ozonides."^{1,3} These typically undergo very rapid cycloreversion to generate a pair consisting of an aldehyde or ketone and a short-lived carbonyl oxide.⁴ The carbonyl oxide generally undergoes one of two reactions: 1) cycloaddition with a carbonyl to furnish "secondary" ozonides (favored under aprotic conditions); or 2) addition of a nucleophile, most often an unhindered alcohol to form hydroperoxyacetals and related addition products.^{1,10} Exceptions to this pattern of reactivity are often encountered with enones, allylic alcohols, and silyl/stannyl alkenes.^{1,3,5} *Caution:* Ozonides and hydroperoxyacetals are typically decomposed to stable products without isolation (see "Workup" section). Although these peroxidic intermediates are frequently isolable, they are capable of self-accelerating decomposition reactions and must be handled with care. The reader is directed to our web-published guide to handling of peroxides.⁶

Figure 2. Mechanism of Alkene Ozonolysis (to initial peroxide products)

Substrate reactivity: Electron density is the most significant predictor of rate, with bimolecular rate constants increasing by up to 10^5 in moving from electron-poor substrates such as acrylates to enol ethers and highly substituted alkenes.¹ However, despite this, selective cleavage within polyunsaturated systems or in the presence of an electron-rich group can be challenging.^{1,7} Selectivity can be enhanced by optimizing reagent distribution (gas delivery device, rapid stirring, reaction dilution), by use of a Sudan dye as an ozone indicator (see below), and/or by reaction in the presence of small amounts of pyridine.⁸

Typical Reaction Conditions: Small-scale reactions often employ a pipette or narrow tube to deliver a gas solution of O_3/O_2 onto or into chilled and stirred reaction solutions. The more effective dispersion made possible by a gas frit or similar device can be useful even on small scale and becomes essential on larger scales. Ozonolysis within flow reactors has also been reported.¹ Reactions are most often conducted in dichloromethane (when ozonides are desired) or mixtures of dichloromethane/methanol (to form intermediate hydroperoxyacetals); see reference 1 for discussions of reactions in other solvents. Although most procedures describe reactions in a $-78\text{ }^\circ\text{C}$ bath, most reactions can be run uneventfully up to $0\text{ }^\circ\text{C}$. *Warning:* Solution ozonolyses should never be attempted at temperatures less than $-95\text{ }^\circ\text{C}$ as condensation ($-112\text{ }^\circ\text{C}$) or freezing ($-193\text{ }^\circ\text{C}$) of ozone in the presence of organics almost guarantees an explosion.

Monitoring: A control run against a known substrate will often allow one to establish the amount of O_3 delivered per unit time under a given set of conditions. The pale blue of solubilized ozone (Fig. 3B) has been often used as an indicator for reaction completion. However, this tinting is only observed at low temperatures and for some solvents. Ozone-sensitive Sudan dyes (compare 3C to 3D below) offer a more reliable indicator of endpoint and can be particularly valuable for selective consumption of an alkene in the presence of another reactive group.^{7,9}

Work-up (see Figure 1). Most ozonolysis reactions are followed by a work-up reaction that destroys the ozonide

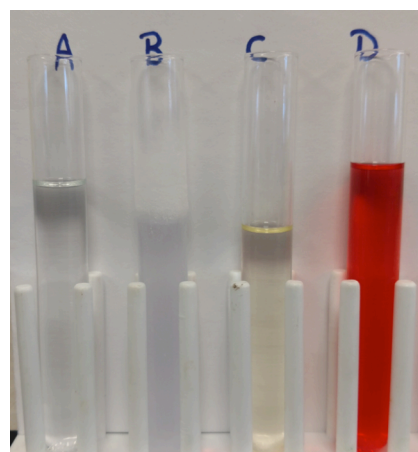


Figure 3. Color changes related to reaction monitoring:

- A) CH_2Cl_2 at rt;
- B) O_3 in CH_2Cl_2 at $-78\text{ }^\circ\text{C}$ (partially obscured by condensation).
- C) Sudan III in CH_2Cl_2 following treatment with O_3/O_2 .
- D) Sudan III in CH_2Cl_2

or hydroperoxyacetal intermediates. A brief summary follows. For more detailed information, the reader is directed to leading references:^{1,10}

Reduction to ketones and aldehydes: Selective reduction to generate aldehydes and ketones has been accomplished with a variety of reagents.¹¹ Hydroperoxyacetals are far more reactive than ozonides, and reduction is often accomplished with triphenylphosphine,¹² thiourea,¹³ dimethyl sulfide.¹⁴ Ozonides can sometimes be reduced using these same reagents but reactions are much slower, and removal of the ozonide should be verified (see "Monitoring") before solutions are concentrated.¹⁵ Ozonides are nearly always susceptible to rapid reduction by zinc/acetic acid or similar "dissolving metal" systems.^{15,16}

Reduction of ozonides or hydroperoxyacetals to alcohols is possible with many common metal hydrides, most often NaBH₄.^{1,17}

"Reduction" via base-promoted fragmentation: Ozonides derived from terminal and 1,1-disubstituted alkenes undergo base-promoted fragmentation under mild conditions (e.g., Et₃N) to directly furnish aldehydes or ketones.¹⁸

Reductive ozonolysis (no work-up): Aprotic ozonolyses conducted in the presence of *N*-oxides or pyridine directly output anhydrous solutions of ketones and aldehydes without formation of peroxide intermediates;^{19,20} the products can be directly applied as substrates for C-C bond-forming processes.²¹ Ozonolysis in the presence of solubilized water also provides moderate to good yields of ketones and aldehydes.²²

Oxidation: The direct conversion of terminal and 1,2-disubstituted alkenes to carboxylic acids, sometimes described as "oxidative ozonolysis", can through treatment of initial ozonolysis products with hydrogen peroxide or other oxidants.^{1,10,23}

Heterolytic fragmentations and rearrangements:^{1,24} Acylation or sulfonation of hydroperoxyacetals containing an adjacent C-H results in dehydration to esters.²⁵ Hydroperoxyacetals lacking an adjacent C-H can undergo C-to-O skeletal rearrangements upon acylation (Criegee rearrangement).²⁶

Homolytic fragmentation: Hydroperoxyacetals and ozonides are both decomposed by Iron salts (typically Fe+2 but sometimes Fe+3) to give "c-1" products through decarbonylation of an

initially generated alkoxy radical.^{1, 27} Depending upon conditions, chlorides, bromides, alkenes, or dimeric products can be generated.

Safety issues.

Prior to performing an ozonolysis, experimenters must consider the reactivity and toxicity of ozone, the exothermicity of the reaction, and the potential of the intermediates and products to undergo self-accelerating and dangerously exothermic decomposition reactions.²⁸

Ozone is highly toxic and negative effects have been associated with long-term exposure to levels of 80 ppb; concentrations in the low ppm range are considered immediately dangerous to life and health.²⁹ As a consequence, most chemistry involving ozone is conducted in an exhaust cabinet or with reaction gases vented through some form of scrubber. Fortunately, most individuals can detect the odor of O₃, sometimes described as "sharp" or "clean", at a concentration of 20 ppb.³⁰ An earlier section of this document warns against conditions that would result in condensation of liquid or solid ozone.

Ozonolyses, which are often highly exothermic reactions conducted in organic solvents under an oxygen-rich atmosphere, are inherently hazardous.^{28,31} The danger of fire has been addressed by removal of headspace oxygen,³² reaction in flow/microchannel systems,³³ or reaction in nonflammable media.³⁴ For reactions on a small scale and conducted in low boiling solvents (e.g. CH₂Cl₂ or CH₃OH/CH₂Cl₂) generated heat is typically cancelled out by rapid evaporative cooling. However, reactions at scale and/or in higher-boiling solvents must be careful to avoid temperature rise and the associated self-accelerating decomposition of peroxide intermediates.¹¹³⁵ As discussed above, it is imperative to avoid formation of liquid or solid ozone.

The potential of the peroxide intermediates or products to undergo self-accelerating decomposition,^{28, 36} combined with the exothermicity of typical work-ups,^{31, 37} makes thermal analysis of reactions and intermediates essential for reactions at even medium scales. For example, differential scanning calorimetry (DSC) has found ΔH for decomposition of a terminal ozonide to be 70-80 kcal/mol, with maximum heat release occurring around 131 °C.³⁸ The use of tools to predict the latent energy of unstable organic compounds has been described.³⁷ The undesired isolation of difficult-to-reduce ozonides be mitigated by reaction in the presence of

methanol to steer reactions towards formation of easily reduced hydroperoxyacetals,^{15b, 39} or by use of a reductive" ozonolyses (described earlier).

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Free link until 8/17/2017: <https://authors.elsevier.com/a/1VHsy9BxJuxZi>

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