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‘Reductive ozonolysis’ via a new fragmentation of carbonyl oxides

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Abstract—This account describes the development of methodologies for ‘reductive’ ozonolysis, the direct ozonolytic conversion of alkenes into carbonyl groups without the intermediacy of 1,2,4-trioxolanes (ozonides). Ozonolysis of alkenes in the presence of DMSO produces a mixture of aldehyde and ozonide. The combination of DMSO and Et_3N results in improved yields of carbonyls but still leaves unacceptable levels of residual ozonides; similar results are obtained using secondary or tertiary amines in the absence of DMSO. The influence of amines is believed to result from conversion to the corresponding *N*-oxides; ozonolysis in the presence of amine *N*-oxides efficiently suppresses ozonide formation, generating high yields of aldehydes. The reactions with amine oxides are hypothesized to involve an unprecedented trapping of carbonyl oxides to generate a zwitterionic adduct, which fragments to produce the desired carbonyl group, an amine, and $^1O_2$.

1. Introduction

The ozonolysis of alkenes, first reported in 1840, remains one of the most important methods for oxidative cleavage of alkenes.[1] For example, a *SciFinder* search for ozone-related conversion of terminal alkenes to aldehydes returns thousands of examples. A powerful oxidant directly available from oxygen, ozone is also an attractive reagent for sustainable oxidations. However, whereas alkene cleavage with high-valent metal oxides typically results in the direct formation of aldehydes and ketones, ozonolysis initially generates ozonides and other peroxides, species often capable of spontaneous and dangerously exothermic decomposition reactions.[2] The formation of energetic intermediates is particularly problematic for large-scale processes, but even laboratory-scale reactions must typically be accompanied by a subsequent work-up reaction, most often a reduction.[3,4] The most effective reducing agents can lead to problems with functional group compatibility (Pt/H_2, BH_3, $Zn/HOAc$, $LiAlH_4$) or product separation (PPh_3).[5] The use of more selective and easily separated reagents (Me_2S) can leave high concentrations of residual 1,2,4-trioxolane (ozonide), leading to explosions upon reaction concentration.[6] We hoped to exploit the mechanism of alkene ozonolysis to achieve the direct production of carbonyl products, avoiding generation or isolation of peroxidic intermediates. In this account, we describe the development of a practical methodology for ‘reductive ozonolysis’ in which trapping and fragmentation of carbonyl oxides by amine oxides results in the direct formation of aldehydes and ketones.[7]

In approaching this problem, it is instructive to overview the mechanism of alkene ozonolysis (Fig. 1).[8] A highly exothermic cycloaddition of ozone with an alkene generates a *primary ozonide* (1,2,3-trioxolane).[9] The primary ozonide has limited stability, and, under typical reaction conditions ($>-80\,^\circ C$) undergoes immediate cycloreversion to a *carbonyl oxide* and a carbonyl. The fate of the carbonyl oxide, which is so short lived as to be undetectable in solution-phase chemistry, determines the distribution of reaction products.[10] A nearly activationless cycloaddition of the carbonyl oxide with a reactive dipolarophile, often the co-generated aldehyde or ketone, produces *ozonides* or 1,2,4-trioxolanes.[11] Alternatively, trapping of carbonyl oxides by unhindered alcohols[12] and related nucleophiles generates hydroperoxyacetals and similar addition products.[8,10] When neither addition nor cycloaddition pathways are available, carbonyl oxides can undergo dimerization or oligomerization to furnish 1,2,4,5-tetraoxanes or polymeric peroxides.[13] For simplicity, only ozonide formation is illustrated.

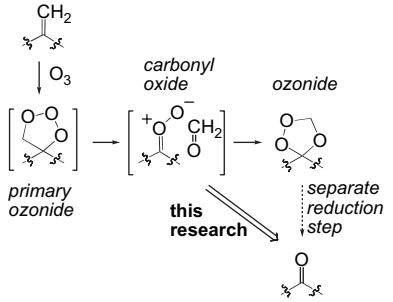

Figure 1. Overview of alkene ozonolysis.

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Ozonides possess a dangerous combination of kinetic stability and thermochemical instability; they are typically isolable yet often capable of spontaneous and dangerously exothermic decomposition reactions.[2] Our goal was to develop methodology that would avoid generation of ozonides or other peroxides, and instead directly deliver the desired carbonyl products. Our approach required a reagent capable of intercepting the primary ozonide, the carbonyl oxide, or the ozonide (1,2,4-trioxolane), yet compatible with ozone, one of the strongest oxidants in organic chemistry. Ozonides appeared too stable to be the targets of such an approach. Primary ozonides (1,2,3-trioxolanes) have been generated at very low temperature and separately reacted with strong nucleophiles, but this process has not been accomplished in the presence of ozone.[14] This leaves carbonyl oxides, the most reactive intermediates in an ozonolysis, as the most logical targets for in situ capture.

2. Results and discussion

Our initial approach focused on cycloaddition of carbonyl oxides with X=O reagents (Fig. 2). An optimal trapping reagent would be a readily available and reactive dipolarophile containing a central atom (X) in an incompletely oxidized state. The derived heteroozonides would be expected to undergo internal fragmentation with liberation of O=X=O and a carbonyl group, achieving net oxidation of the X=O reagent and net reduction of the carbonyl oxide. Literature reports suggested that sulfinyl dipolarophiles reduce carbonyl oxides, presumably via intermediate 3-thia-1,2,4-trioxolanes.[15] Moreover, electron rich carbonyl oxides preferentially oxidize sulfoxides (to sulfones), even in the presence of a sulfide.[16] A similar strategy has recently been applied to the reduction of persulfoxides with aryl selenoxides.[17]

Our investigations began with dimethyl sulfoxide (DMSO). Whereas ozonolysis of decene provides a nearly quantitative yield of isolated ozonide (3-octyl-1,2,4-trioxolane),[18] the same reaction in the presence of 2.0 equiv of DMSO generated a mixture of aldehyde and ozonide in which the former was predominant (Table 1). While these results were intriguing, we were unable to find conditions able to effectively suppress ozonide formation. For example, the use of 5 equiv of DMSO offered little improvement in yield of aldehyde,[19] while attempts to employ even larger amounts of reagent resulted in phase separation or freezing.

The addition of protic nucleophiles provided an opportunity to test the role of the carbonyl oxide in the DMSO-promoted reductions (Table 2). The presence of methanol resulted in the formation of hydroperoxyacetal at the expense of aldehyde. The same effect was observed to a lesser extent for isopropanol, as would be expected based upon the reported rates of trapping by primary and secondary alcohols.[10,12]

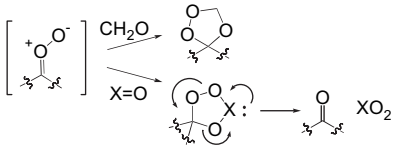
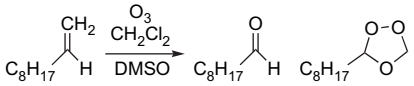


Figure 2. Capture by reductive dipolarophile.

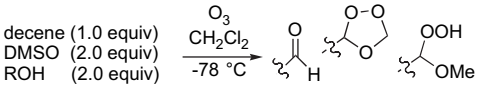
Table 1. Reduction with DMSO



DMSO (equiv)	T (°C)	Aldehyde (%)[a]	Ozonide (%)[a]
0	−78 or 0	Trace	>95%
2	−78	52	35
2	0	61	22

[a] Isolated yield.

Table 2. Competition for carbonyl oxide



ROH	Aldehyde (%)[a]	Ozonide (%)[a]	Hydroperoxide (%)[a]
MeOH	11	16	31
i-PrOH	34	19	23

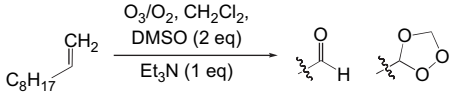
[a] Isolated yield.

The DMSO-mediated reduction was unaffected by the addition of a proton donor (HOAc), but was actively suppressed by $Sc(OTf)_3$. Although we had hoped that the Lewis acid might serve to bring together the reactants, the results suggest that the Sc^{+3} is simply sequestering the sulfoxide. In contrast, ozonolysis at −78 °C in the presence of both DMSO and Et_3N achieved a noticeable improvement in the yield of aldehyde (Table 3); an even better yield was obtained upon reaction at 0 °C. The formation of aldehyde appeared to be enhanced by trace moisture; performing the reaction with deliberate exclusion of water (including drying the incoming stream of O_3/O_2 through a −78 °C U-tube), resulted in a reduced yield. For reasons that would later become clear, the use of excess Et_3N slowed the reaction and resulted in the isolation of recovered decene (not shown).

The combination of DMSO and Et_3N provides a useful protocol for syntheses of aldehydes and ketones (Table 4).

To our surprise, a control reaction investigating ozonolysis in the presence of Et_3N furnished better yields of nonanal than had been obtained with DMSO (Table 5). The amine-promoted reduction appeared general for secondary and tertiary amines; primary amines, which react with carbonyl oxides to form oxaziridines, were not investigated.[20] The use of anhydrous conditions again resulted in a decreased yield of aldehyde.

Table 3. Reaction with DMSO and Et_3N



T (°C)	Wet/dry	Aldehyde (%)[a]	Ozonide (%)[a]
−78	Dry	43	17
−78	Wet[b]	65	29
0	Wet	84	12

[a] Isolated yield.
[b] H_2O (0.05%) in CH_2Cl_2.