

‘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 Et₃N 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 ¹O₂.
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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/H₂, BH₃, Zn/HOAc, LiAlH₄) or product separation (PPh₃).⁵ The use of more selective and easily separated reagents (Me₂S) 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 °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 alcohols¹² 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.

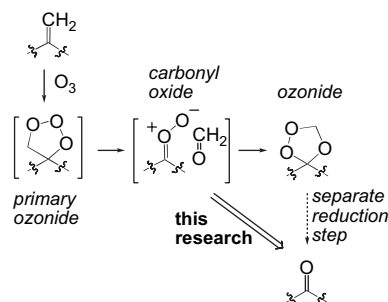


Figure 1. Overview of alkene ozonolysis.

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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}

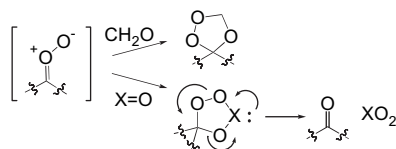


Figure 2. Capture by reductive dipolarophile.

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>i</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 .

Table 4. Application to other substrates

Alkene	$\xrightarrow{\text{O}_3^a}$	carbonyl ^b	ozonide ^b
	\longrightarrow	 93%	 trace
	\longrightarrow	 65%	 28%
	\longrightarrow	 64%	 7%

^a O_3 , DMSO (2 equiv), Et_3N (1 equiv), wet CH_2Cl_2 , 0 °C.^b Isolated yield.

The sole precedent for this process was a report describing isolation of adipaldehyde upon ozonolysis of cyclohexene in the presence of Et_3N .²¹ The reduction of carbonyl oxides by pyridine has been reported and later refuted.²² However, several observations led us to question the role of the amines. First, as had been previously observed during the experiments with DMSO/ Et_3N , the use of excess amine slowed consumption of alkene. Second, directing the gaseous stream of O_3/O_2 onto or into a CH_2Cl_2 solution of alkene and amine resulted in intense fuming, which persisted for a period proportional to the amount of amine. Similar fuming was observed for ozonolysis of solutions of Et_3N or *N*-methylmorpholine (NMM); in contrast, no fuming was observed when a stream of ozone was directed onto or into a solution of decene. Moreover, monitoring (TLC or NMR of quenched aliquots) of the ozonolysis of mixtures of amine and alkene detected very little formation of aldehyde or ozonide until after fuming had ceased. Third, ozonolysis of a solution of amine, followed by addition of decene and continued ozonolysis, produced a mixture of aldehyde and ozonide. These results suggested the intermediacy of *N*-oxides. The ozonolysis of tertiary amines is known to

Table 5. Ozonolysis in presence of amines

Amine	T (°C)	Wet/dry	Aldehyde (%)	Ozonide (%)
Et_3N	−78	Wet ^a	79	13
Et_3N	−78	Dry	50	30
Et_3N	0	Wet	75	14
Et_3N (2 equiv)	0	Wet	64 ^b	14
NMM	0	Wet	68	12
NMM	0	Dry	57	10
Morpholine	0	Wet	62	10
Morpholine	0	Dry	56	18
EtNi-Pr_2	0	Dry	58	9
$(\text{C}_{12}\text{H}_{25})_2\text{NMe}$	0	Wet	55	15
DABCO	0	Dry	48	10
Pyridine		Dry	16	11

^a H_2O (0.05%) in CH_2Cl_2 .^b Unreacted alkene also recovered.

furnish both *N*-oxides and products of side chain cleavage, the latter process accounting for our observation of acetaldehyde in the crude products from reactions employing Et_3N .²³ Furthermore, the ratio of *N*-oxide formation to side chain cleavage is enhanced in the presence of a proton donor, accounting for the influence of moisture on the reactions involving amines.

The role of *N*-oxides was explicitly tested by ozonolysis of 1-decene in the presence of commercial *N*-methylmorpholine-*N*-oxide (NMMO). Reaction proceeded without fuming to furnish *exclusively* nonanal (Table 6).²⁴ Predominant formation of aldehyde was also observed for reactions in the presence of DABCO-*N*-oxide and pyridine *N*-oxide. The latter reduction, while complicated by the formation of intensely colored byproducts, is noteworthy given the very limited amount of reduction observed in the presence of pyridine.

The intermediacy of carbonyl oxides in these reactions was supported by a simple set of competition reactions. The products obtained from ozonolysis of a CH_2Cl_2 solution of decene were compared under three sets of conditions: (1) no additives; (2) addition of stoichiometric MeOH; and (3) addition of stoichiometric amounts of both MeOH and NMMO (Table 7). The results demonstrate competition between the amine oxide and the alcohol for capture of the intermediate nonanal-*O*-oxide.²⁵ Furthermore, 1-methoxydecene, which generates the same carbonyl oxide but cannot easily form an ozonide, also produces nonanal as the major product in the presence of NMMO.¹⁰

Table 6. Reduction by amine oxides

Amine oxide (equiv)	T (°C)	RCHO (%) ^a	Ozonide (%) ^a
NMMO (1.0)	−78 or 0	88	0
NMMO (3.0)	0	94	0
Et_3NO^b (1.0)	0	80	Trace
Me_3NO^c (1.0)	0	68	12
DABCO- <i>N</i> -oxide (1.0)	0	62	10
Pyridine <i>N</i> -oxide (1.0)	0	58	9

^a Isolated yields.^b Generated in situ.^c Poor solubility.**Table 7.** Competition for the carbonyl oxide^a

X	Additive	A	B	C
H	None	—	—	Major
H	MeOH	Trace	Major	Minor
H	MeOH+NMMO	Major	Minor	Trace
OMe	MeOH+NMMO	Major	Trace	Trace

^a Ratios assessed by ^1H NMR of reaction mixtures.

2.1. Role of base-promoted fragmentation

Amines and pyridines are known to cleave terminal ozonides to a 1:1 mixture of aldehyde and formate through a Kornblum-type E_1CB fragmentation (Fig. 3).^{26–28} Although amine oxides are less basic than amines,²⁹ we were curious as to whether the putative reductions might also result from base-promoted fragmentation. In fact, treatment of a CH_2Cl_2 solution of purified decene ozonide with NMMO did generate a 1:1 mixture of nonanal and formate. However, the reaction was slower than the in situ reductions described above. More convincingly, analysis of the crude reaction mixtures from ozonolysis of decene in the presence of NMMO consistently found ratios of aldehyde/formate greater than 4:1, indicating that the base-promoted fragmentation is a minor contributor to the direct formation of aldehyde in the ozonolysis medium.

However, the base-promoted fragmentation may serve a useful role as a scavenging reaction. For example, if the solution resulting from ozonolysis of a mixture of decene and NMMO (1.0 equiv) is quenched into pH 6 buffer prior to concentration, a small amount of ozonide (up to 7%) is isolated; in the absence of an acidic quench, no ozonide is present after concentration. If the reaction is conducted with three or more equivalents of NMMO, no ozonide is observed regardless of work-up, suggesting that capture of the carbonyl oxide is complete at the higher reagent concentration. For more substituted systems such as the ozonides of methyl oleate (vida infra), the base-promoted fragmentation is much slower, and even less likely to play a significant role in the formation of aldehydes during ozonolysis.

2.2. Other substrates

In situ reduction was successfully applied to the ozonolysis of a 1,2-disubstituted alkene, methyl oleate; the disparity in the isolated yields of the two products appears to result from the volatility of nonanal (Fig. 4). Application of the same protocol to 2-methylundecene provided a moderate yield of 2-undecanone as well as a number of unidentified minor byproducts; similar results were obtained for other 1,1-disubstituted alkenes (not shown). The lower yield observed for a ketone compared with aldehydes could result from a lower efficiency of nucleophilic addition to the ketone



Figure 3. Base-promoted fragmentation.

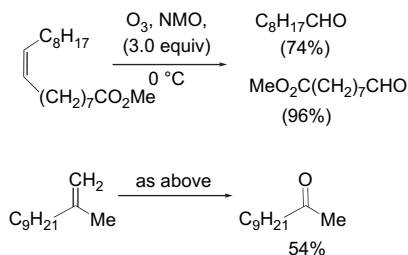


Figure 4. Other substrates.

O -oxide, allowing more time for side reactions such as tautomerization or polymerization.¹⁰ We continue to investigate this process in the hope of identifying optimal conditions for ketone synthesis.

2.3. Mechanism

There is no mechanistic precedent for ‘reductive’ ozonolysis in the presence of amine oxides. Our hypothesis is that the process is not actually a reduction, but instead a fragmentation driven by the reactivity of carbonyl oxides (Fig. 5). Nucleophilic addition of the amine oxides generates an unstable zwitterionic peroxyacetal, which undergoes decomposition to generate aldehyde or ketone, amine, and dioxygen. The proposed mechanism bears a topological resemblance to the Grob fragmentations of diol monosulfonates³⁰ and to the conversion of ketones to dioxiranes.³¹

Verification of the mechanism may prove challenging. Quantification of the liberated amine will be complicated by rapid oxidation by ozone. Decomposition of a ground state zwitterion would be expected to liberate dioxygen in the singlet state; however, detection of 1O_2 will be constrained by the compatibility of probe molecules with ozone. Although an alternative route to carbonyl oxides is available through photosensitized oxidation of diazoalkanes,³² the amine produced by the predicted mechanism would quench 1O_2 and suppress the photooxidation. The extent of transfer of ^{18}O from a labeled amine oxide to the carbonyl products would provide unambiguous evidence for the proposed mechanism. However, no preparation of a labeled amine oxide has been reported and we were unable to find a method for oxidation of tertiary amines that would be practical for use of ^{18}O -labeled reagents.

The success of the reductive ozonolysis reflects attributes of both carbonyl oxides and amine oxides. Carbonyl oxides are highly reactive species typically represented as either zwitterions or diradicals.¹⁰ Although calculations suggest that the diradical is more representative of gas phase structure, our previous work demonstrated the ability to exploit the zwitterionic character to enhance additions of nucleophiles.³³ Amine oxides are not only nucleophilic but also contain an easily fragmented $N-O$ bond, characteristics that form the basis of a conversion of activated halides to aldehydes.³⁴ In addition, the coordinative saturation of the

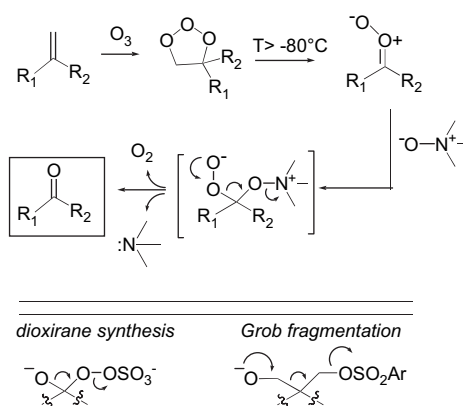


Figure 5. Proposed mechanism.

ammonium leaving group blocks heteroozonide formation, leaving fragmentation as the most favorable option. The successful reductions in the presence of morpholine (Table 5) suggests that either hydroxylamines or nitrones may also promote a similar fragmentation.³⁵

While the oxidative regeneration of the amine oxide would seem to offer the possibility of catalytic reactions, the need to competitively capture the carbonyl oxide sets a realistic lower threshold on the concentration of reagent. Moreover, the lower yields of aldehyde obtained for ozonolyses in the presence of stoichiometric NMM (Table 5) versus NMMO (Table 6) may reflect not only the competing formation of ozonide during early stages of the reaction (when amine oxide concentration is necessarily low) but also the fact that the ozonolysis of amines furnishes amine oxides in less than quantitative yields.³⁶ However, regeneration of amine oxides may hold promise in batch reactions and for regeneration of supported reagents.

Finally, the observed fragmentation of carbonyl oxides could be the first example of a new class of reactions. The key structural feature in the amine oxides, a nucleophilic center weakly bonded to a leaving group, is found in other α -nucleophiles, suggesting that a similar fragmentation may be possible with reagents such as hypohalites and peroxysulfates (Fig. 6). Along these lines, it is interesting to note that reaction of amine oxides with dioxiranes generates amines and $^1\text{O}_2$, presumably via an intermediate peroxyammonium zwitterion.³⁷

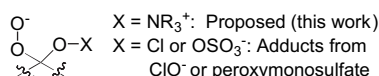


Figure 6. Alternative fragmentation precursors.

3. Conclusion

The ozonolysis of alkenes in the presence of amine oxides directly generates aldehydes and ketones through an unprecedented mechanism involving nucleophilic trapping of carbonyl oxides and fragmentation of the derived zwitterionic peroxides. The methodology, which avoids formation of ozonides or related energetic intermediates, offers a safer alternative to traditional ozonolyses and may expand the synthetic applications of an already versatile oxidative cleavage.

Acknowledgements

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24. Typical procedure: to a dry 100-mL round bottom flask was added 3.0 mmol of decene, 20 mL of methylene chloride, and 9.0 mmol of *N*-methylmorpholine-*N*-oxide (NMMO). The stirred solution was cooled to 0 °C and a solution of 2% O₃/O₂ (nominal output of 1 mmol O₃/min) was introduced directly above the solution via a glass pipette for 6.6 min (nominally 2.2 equiv ozone relative to alkene). This mode of ozone addition furnished the most consistent results. The solution was then sparged with O₂ for 2 min and warmed to room temperature. Following confirmation of the absence of ozonide (TLC), the solution was concentrated and the residue was purified by flash chromatography using 5% diethyl ether/pentane. Alternatively, the crude reaction was quenched into pH 6 phosphate buffer and extracted with ether prior to concentration and chromatography.
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