Ozonolysis in Solvent/Water Mixtures: Direct Conversion of Alkenes to Aldehydes and Ketones

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Ozonolysis of alkenes in the presence of solubilized water results in the direct formation of aldehydes and/or ketones, avoiding the need to isolate or decompose ozonides.

Ozonolysis is a powerful and popular method for the oxidative cleavage of alkenes, with thousands of reported examples.[1,2] However, under typical conditions, alkene ozonolysis initially generates ozonides or hydroperoxyacetals, which must be reduced in a separate step to obtain the desired aldehydes or ketones.[1,3,4] The formation of intermediates potentially capable of spontaneous and exothermic decomposition can be problematic, particularly for preparative reactions.[5] The initial reaction products from ozonolyses are therefore typically reduced to carbonyl compounds in a separate postozonolysis step. However, the use of mild reductants such as Me_2S carries the risk of incomplete removal of ozonides,[5] while more powerful reductants (Pt/H_2, BH_3, Zn/HOAc, $LiAlH_4$) may be incompatible with other functional groups or may complicate product purification.[6–8]

In approaching this problem it is useful to overview the pathways for peroxide formation (Figure 1).[1,3,9] The highly exothermic addition of ozone to alkenes generates primary ozonides (1,2,3-trioxolanes), which fragment, even at −80 °C, to form carbonyl oxides. The fate of these short-lived intermediates determines the distribution of the observed products. Cycloaddition of carbonyl oxides with a reactive dipolarophile,
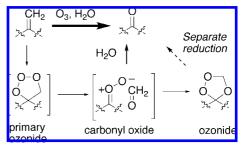

FIGURE 1. Alkene ozonolysis: traditional vs one-step approach.

often the aldehyde or ketone coproduced during the scission of the primary ozonide, forms ozonides (1,2,4-trioxolanes).[4] Alternatively, trapping by unhindered alcohols and other related nucleophiles generates hydroperoxyacetals and similar addition products.[3,10] When the carbonyl oxides cannot undergo addition or cycloaddition, dimerization or oligomerization yields 1,2,4,5-tetraoxanes or polymeric peroxides.[11]

We became interested in practical methodology for preparative trapping of carbonyl oxides by water. Assuming the intermediate hydroperoxy hemiacetals would decompose under the reaction conditions, the net result would be the direct formation of carbonyl groups during ozonolysis (Figure 1). However, while the gas-phase trapping of carbonyl oxides by water has been extensively investigated,[12] there are only a handful of corresponding solution-phase studies and little indication of whether water trapping can provide a useful preparative alternative to conventional ozonolyses.[10,13] We now report that the ozonolysis of alkenes in the presence of solubilized water offers a means for the direct synthesis of aldehydes and ketones.

Our research grew from investigations of "reductive ozonolyses".[14] The mechanism proposed for this transformation, involving fragmentation of the tetrahedral intermediate derived from addition of amine oxides to carbonyl oxides, suggested a similar reaction might occur in the presence of any reagent containing a nucleophilic oxygen weakly bonded to a potential leaving group. As a test of this hypothesis, we investigated biphasic ozonolysis of a mixture of 9-decenyl acetate and sodium periodate in CH_2Cl_2/H_2O under phase-transfer conditions (Table 1). While initial results were promising, a similar yield of aldehyde was obtained from a control reaction omitting periodate. In contrast, a reaction including periodate but lacking

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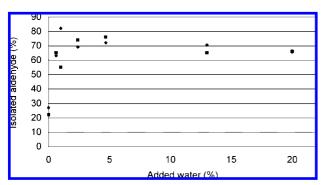
FIGURE 2. Yield of 9-acetoxynonanal upon ozonolysis of decenyl acetate in solvent/water mixtures: ■ = acetone; ◆ = acetonitrile.

TABLE 1. Ozonolyses of 9-Decenyl Acetate[a]

PTC	additive	% H_2O (v/v)	ozonide (%)	aldehyde (%)
Bu₄NBr	NaIO₄	5	9	42
Bu₄NBr	none	5	9	51
none	none	5	13	29
none	none	0	72	13

[a] See the Experimental Section.

the phase-transfer catalyst (PTC) resulted in low yields for both the aldehyde and ozonide; a similar outcome was obtained in biphasic CH_2Cl_2/H_2O in the absence of both periodate and the PTC. These results suggested that solubilized water was an effective nucleophile toward carbonyl oxides.

We therefore elected to investigate ozonolysis of alkenes in miscible water/organic mixtures (Figure 2). As our initial solvent, we selected acetone, an inexpensive, low-boiling, and ozone-stable solvent. Ozonolysis of 9-decenyl acetate in solutions of water and reagent grade acetone revealed formation of aldehyde to be the dominant pathway over a range of added water. Ozonide formation was almost completely suppressed in 5% H_2O/acetone (v/v) and this solvent was used for most subsequent reactions. An analogous series of ozonolyses in H_2O/acetonitrile mixtures generated nearly identical results, suggesting the role of the polar solvent is simply to solubilize water. Monitoring the reactions (NMR, aliquots removed at 0.55 min intervals) demonstrated that the carbonyl product is generated immediately and with a stoichiometry proportional to the disappearance of alkene (Figure 3); only traces of ozonide could be detected at any point in the reaction.

At this point we set out to test the methodology on a series of synthetically relevant substrates (Table 2). Ozonolysis was performed until the alkene was consumed, based upon the end point of a Sudan III indicator.[15] Products were isolated after extraction, with no separate reduction. The results vary with the structure of the substrate. Ozonolyses of terminal alkenes (products **1**, **2**, **5**, and **6**) generate aldehydes in yields of 72–100%. Ozonolysis of a 1,1-diaryl alkene (product **3**) proceeded in moderate yield. The corresponding cleavage of a 1,1-dialkyl-substituted alkene (product **4**) provided a quantitative yield of ketone on 3 mmol scale, with a slightly lower yield obtained on a preparative scale (the Supporting Information includes a description of a preparative reaction employing a distillative purification).
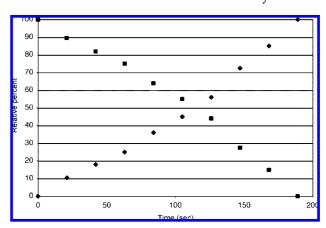

FIGURE 3. Relative proportions of alkene and aldehyde during ozonolysis of 9-decenyl acetate in H_2O/acetone: ■ = 9-acetoxynonanal; ◆ = 9-decenyl acetate
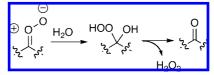

FIGURE 4. Proposed reaction mechanism.

TABLE 2. Direct Ozonolytic Preparation of Carbonyl Compounds

entry	compound		isolated yield[a]
	AcO~~~X	1	72%
	Bz-O~~~X (with X)	2	75%
	Ph₂C=X	3	54%
	cyclohexanone deriv	4	100% (86%)[b] (78%)[c]
	R-C₆H₄-CH=X, R = OAc	5	81%
	R = NO₂	6	100%

[a] Addition of 2% O_3/O_2 into a 0.15 M solution of alkene (3 mmol). [b] 20 mmol scale. [c] 30 mmol scale with distillation of product.

The addition of water to carbonyl oxides is believed to generate a *gem*-hydroperoxy alcohol, which for most substrates decomposes with liberation of the aldehyde or ketone and H_2O_2 (Figure 4).[1,12,13] Monitoring of our reactions with a redox-active TLC indicator invariably detected the build-up of a substantial quantity of H_2O_2.[16] A more quantitative postreaction assay, conducted by testing the separated aqueous layer with peroxide test strips, detected a stoichiometric amount of H_2O_2 relative to the consumed alkene.[17] In contrast, a control experiment involving ozonolysis of a solution of 5% H_2O/acetone in the absence of alkene generated barely detectable quantities of H_2O_2.

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Ozonolysis of alkenes in a mixture of water and a water-miscible organic solvent achieves a fast, convenient, and efficient one-pot synthesis of aldehydes and ketones without the need for a separate reductive step. In contrast to the time required for a traditional ozonolysis and workup,[5–8] the new procedure generates the carbonyl products at rates limited only by the output of the ozonizer. While the trapping of carbonyl oxides by water has been previously observed, this reaction has not to our knowledge been studied as a preparative organic method. We believe the procedures outlined in this paper will lead to broader application of ozonolysis, a metal-free oxidation requiring only electricity and oxygen.

Experimental Section

Standard Conditions for Ozonolysis. The alkene substrate (3 mmol) was placed in a round-bottomed flask and dissolved in 95:5 acetone/water (v/v) to a concentration of 0.15 M. Following addition of a small amount of an acetone stock solution of Sudan Red III,[15] the solution was cooled to 0 °C and a stream of O_3/O_2 (2%, approximately 0.5 mmol/min O_3) was bubbled into the reaction solution through a disposable pipet. Once the color of the indicator was discharged, the ozonizer voltage was set to zero, and the reaction was sparged for 2 min with O_2. The crude reaction mixture was worked up by one of two procedures, either of which afforded similar results: (A) The solution was diluted with 50 mL of pentane and 3 mL of brine. The separated aqueous layer was extracted with 5 mL of pentane and the organic layers were dried over Na_2SO_4.

The residue obtained upon concentration was purified via flash chromatography with ether/hexanes to afford the target aldehyde or ketone. (B) The reaction solution was diluted with 25 mL of water and the resulting mixture was extracted with CH_2Cl_2 (2 × 25 mL), with the remaining workup identical with that described above. An alternate workup employing distillation for product purification is described in the Supporting Information.

Caution. The workup procedures described above may leave the product aldehyde or ketone contaminated with a small amount of residual H_2O_2. For large-scale reactions, an additional water or brine wash will generally reduce the concentration of H_2O_2 to levels below what can easily be detected with peroxide test strips. Experimenters should be aware that concentrated solutions of H_2O_2 and carbonyl groups can undergo acid-promoted reaction to form explosive dimers (1,2,4,5-tetraoxanes) and trimers (1,2,4,5,7,8-hexaoxanes).[18] Although we never detected the formation of cyclic peroxides, experimenters should avoid strongly acidic conditions during the ozonolysis or the workup, and should consider adding a small amount of Ph_3P or a smilar reductant to crude products prior to preparative distillations.

Supporting Information Available: Experimental procedures and ^{1}H for **1** and **4**; ^{13}C spectra of **1−6**. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) The concentration of liberated H_2O_2 corresponds to approximately 0.15 M in the reaction medium, and less than 1 M (approximately 2.5% v/v) in the brine wash. The recovered H_2O_2 can be destroyed by treatment with bisulfite or sulfite; however, many localities permit dilute aq H_2O_2 to be discarded into the sanitary sewer. Storage or acidification of the aqueous layers should be avoided (see the cautionary note in the Experimental Section).

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