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Fragmentation of Carbonyl Oxides by *N*-Oxides: An Improved Approach to Alkene Ozonolysis

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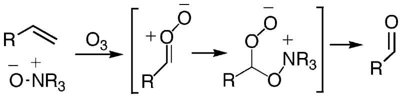
ABSTRACT

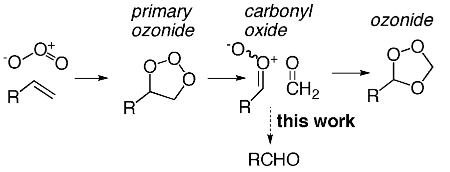


Ozonolysis of alkenes in the presence of amine *N*-oxides results in the direct formation of aldehydes. This reaction, which appears to involve an unprecedented trapping and fragmentation of the short-lived carbonyl oxide intermediates, avoids the hazards associated with generation and isolation of ozonides or other peroxide products.

Although ozonolysis of alkenes to produce carbonyl compounds is a traditional and powerful synthetic transformation,[1,2] its utility is often limited by safety concerns.[3] The 1,2,4-trioxolane (ozonide) products are typically capable of spontaneous and exothermic decomposition, yet are often reduced slowly by mild reducing agents;[4] their persistence following incomplete reduction has resulted in explosions.[5] We sought a new approach to alkene ozonolysis that would avoid generation or accumulation of peroxide products.[6] We now report a “reductive ozonolysis” based upon capture and directed fragmentation of carbonyl oxides by amine *N*-oxides.

Cycloaddition of ozone with an alkene furnishes a 1,2,3-trioxolane (primary ozonide), which undergoes low-temperature cycloreversion to carbonyl oxide and carbonyl fragments. Carbonyl oxides are reactive intermediates able to enter into a number of reaction pathways,[7−9] including cycloaddition with an aldehyde or ketone to form 1,2,4-trioxolanes (ozonides), addition of unhindered protic nucleophiles, or oligomerization. Our goal was the discovery of reagents capable of intercepting and reducing carbonyl oxides during a typical ozonolysis reaction (Scheme 1, illlustrated for aprotic conditions).

Scheme 1. Overview of Alkene Ozonolysis



A report describing the production of adipaldehyde upon ozonolysis of cyclohexene in the presence of Et_3N drew our attention to the potential of tertiary amines as reductants.[10]

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(1) Lee, D. G.; Chen, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 7, p 544.

(2) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. 1.

(3) Kula, J. *Chem. Health Safety* **1999**, *6*, 21; Gordon, P. M. *Chem. Eng. News* **1990**, *68*, 2.

(4) See, for example: Chen, L.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 7561. The use of more effective reducing agents such as PPh_3 (Griesbaum, K.; Kiesel, G. *Chem. Ber.* **1989**, *122*, 145. Clive, D. L. J.; Postema, M. H. D. *J. Chem. Soc., Chem. Commun.* **1994**, 235), BH_3 (Flippin, L. A.; Gallagher, D. W.; Jalali-Araghi, K. *J. Org. Chem.* **1989**, *54*, 1430), $LiAlH_4$ (Greenwood, F. L. *J. Org. Chem.* **1955**, *20*, 803), $NaBH_4$ (Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1952**, *74*, 3855), and Mg/MeOH or Zn/HOAc (Dai, P.; Dussault, P. H.; Trullinger, T. K. *J. Org. Chem.* **2004**, *69*, 2851) can lead to problems with separation of byproducts or functional group compatibility. For an overview of ozonide reduction, see: Kropf, H. In *Houben-Weyl Methoden Der Organische Chemie*; Kropf, H., Ed.; Georg Thieme Verlag: Stuttgart, 1988; Volume E13/2, pp 1111−1114.

(5) Lavallée, P.; Bouthillier, G. *J. Org. Chem.* **1986**, *51*, 1362, footnote 27.

(6) Ozonolysis of electron-poor alkenes in methanolic base results in the direct formation of methyl esters: Marshall, J. A.; Garofalo, A. W.; Sedrani, R. C. *Synlett* **1992**, 643.

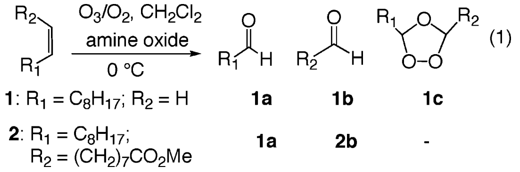
10.1021/ol061001k CCC: \$33.50

As a model system, we selected ozonolysis of decene.[11] Terminal alkenes are common ozonolysis substrates; moreover, the rapid cycloaddition of the derived aldehyde *O*-oxide/formaldehyde pair provides a realistic benchmark against which to measure the efficacy of a reductant.[12] Ozonolysis of decene in the presence of triethylamine, *N*-methylmorpholine, or other tertiary amines did in fact produce nonanal as the major product but invariably contaminated with 10−30% of residual ozonide.

Several observations led us to question whether the amines were the actual reducing agents. First, in contrast to a typical alkene ozonolysis, reactions were accompanied by intense fuming persisting for a period proportional to the amount of added amine; during this interval, we observed little formation of ozonide or aldehyde (TLC or NMR of quenched aliquots). Second, ozonolysis of solutions of amines resulted in similar fuming. Third, addition of decene to a solution of ozone-treated amine, followed by resumption of ozonolysis, afforded nonanal as the major product. Amines are known to react efficiently with ozone, and we began to suspect that the active reagents might be amine oxides generated in situ.[13] We therefore reinvestigated ozonolysis of 1-decene in the presence of stoichiometric *N*-methylmorpholine *N*-oxide (NMMO). The reaction proceeded without fuming to furnish, after concentration and chromatography, a high yield of nonanal and no detectable ozonide (Table 1).

The use of excess NMMO resulted in a slightly improved yield of aldehyde. Reduction was also achieved using pyridine *N*-oxide or DABCO *N*-oxide.[14,15] The method was also effective for ozonolysis of methyl oleate, a 1,2-disubstituted alkene.

Table 1. Ozonolysis in the Presence of *N*-Oxides (eq 1)

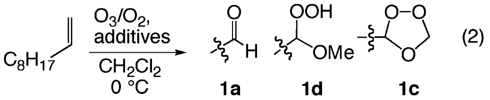


substrate	*N*-oxide (equiv)	aldehyde (yield, %)[a]	ozonide (yield, %)[a]
1	none	trace	**1c** (90)
1	NMMO (1.0)	**1a** (88)	
1	NMMO (3.0)	**1a** (94)	
1	NMMO (5.0)	**1a** (94)	
1	pyridine *N*-oxide (5.0)	**1a** (78)	
1	DABCO *N*-oxide (5.0)	**1a** (79)	
2	NMMO (1.0)	**1a** (74) **2b** (96)	

[a] Isolated yields.

The formation of aldehydes could in theory result from reaction of the amine oxides with the primary ozonide, the carbonyl oxide, or the ozonide. However, the product distributions obtained for ozonolysis of decene, decene and methanol, or decene and methanol and NMMO, suggest a competition for the carbonyl oxide (Table 2). Methoxydecene, which undergoes ozonolysis via the same nonanal *O*-oxide intermediate but cannot easily form an ozonide,[7] also furnishes mainly nonanal upon reaction in the presence of NMMO (not shown).

Table 2. Competition Reactions (eq 2)



additive(s)	**1a** (%)	**1d** (%)	**1c** (%)
none			90−95
MeOH (1 equiv)	trace	66	10
MeOH (1 equiv) + NMMO (1 equiv)	70	20	trace

NMMO does promote a slower base-promoted fragmentation of decene ozonide to furnish a 1:1 mixture of nonanal and formate; an analogous reaction is known for amines.[16] This fragmentation is a minor contributor to the formation of aldehyde during ozonolysis in the presence of amine oxides, as the crude reaction mixtures consistently featured ratios of aldehyde/formate > 4:1. However, the base-promoted process may serve to scavenge traces of residual ozonide. For example, if the crude reaction mixture from ozonolysis of decene and NMMO is washed with pH 6 buffer prior to concentration and purification, a small amount (up

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(7) Bunnelle, W. H. *Chem. Rev.* **1991**, *91*, 335.

(8) Kuczkowski, R. L. *Chem. Soc. Rev.* **1992**, *21*, 79.

(9) Barton, M.; Ebdon, J. R.; Foster, A. B.; Rimmer, S. *J. Org. Chem.* **2004**, *69*, 6967.

(10) Pokrovskaya, I. E.; Ryzhankova, A. K.; Menyailo, A. T.; Mishina, L. S. *Neftekhimiya* **1971**, *11*, 873−8 (CAN 76: 71953).

(11) Any work involving peroxides should follow standard precautions: Medard, L. A. *Accidental Explosions: Types of Explosive Substances*; Ellis Horwood Ltd.: Chichester, 1989; Vol. 2. Patnaik, P. *A Comprehensive Guide to the Hazardous Properties of Chemical Substances*; Van Nostrand Reinhold: New York, 1992. Shanley, E. S. In *Organic Peroxides*; Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. 3, p 341.

(12) The rate of ozonide formation varies with the carbonyl oxide/carbonyl pair. For ozonolysis of terminal alkenes (aldehyde *O*-oxides and formaldehyde), 1,1-disubstituted alkenes (ketone *O*-oxides and formaldehyde), and 1,2-disubstituted alkenes (aldehyde *O*-oxides and aldehydes), cycloaddition is rapid and ozonides are the predominant products under aprotic conditions. See ref 7 for more details.

(13) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. 2, pp 155−201. Maggiolo, A.; Niegowski, S. J. In *Ozone Chemistry and Technology*; American Chemical Society: Washington, DC, 1959; pp 202−204.

(14) **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. The stirred solution was cooled to 0 °C, and a solution of 2% O_3/O_2 (nominal output of 1 mmol O_3/min) was introduced directly above the solution via a glass pipet 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 O_2 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 chromatography.

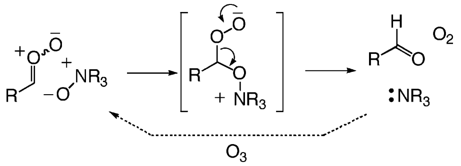
(15) NMMO and pyridine *N*-oxide were used as received. DABCO *N*-oxide was generated in situ by ozonolysis of the amine prior to the addition of alkene.

(16) Hon, Y. S.; Lin, S.-W.; Lu, L.; Chen, Y.-J. *Tetrahedron* **1995**, *51*, 5019.

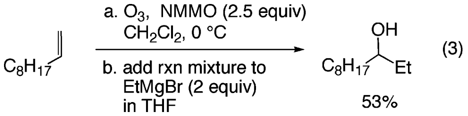
to 7%) of ozonide is isolated. In the presence of three or more equivalents of NMMO, no ozonide is observed regardless of workup procedure, suggesting that capture of the carbonyl oxide is complete at the higher reagent concentration.

To our knowledge, there is no precedent for the observed fragmentation. The most likely mechanism involves nucleophilic addition of the amine oxide to the carbonyl oxide to generate an unstable zwitterion, which fragments to liberate aldehyde, dioxygen, and amine (Scheme 2). In the presence of ozone, the liberated amine undergoes oxidation to regenerate both amine oxide as well as cleavage products derived from side-chain oxidation,[13,17] accounting for our initial results with trialkylamines as well as the superiority of the amine oxides as reagents.

Scheme 2. Proposed Mechanism for Fragmentation



Finally, the in situ reduction holds obvious potential for tandem reaction sequences; an unoptimized example is illustrated in eq 3.



In summary, we have demonstrated a protocol for "reductive“ ozonolysis in the presence of amine oxides. This reaction, the first example of a new class of transformations harnessing the reactivity of carbonyl oxides, offers a safer approach to alkene ozonolysis. Further investigations into the scope, mechanism, and synthetic utility of this transformation are in progress.

Acknowledgment. This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Supporting Information Available: ^{1}H NMR spectra for **1a**,**c**,**d**, **2b**, DABCO, DABCO *N*-oxide, and 3-undecanol. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061001K

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(17) Bailey, P. S.; Lerdal, D. A.; Carter, T. P., Jr. *J. Org. Chem.* **1978**, *43*, 2662.