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Letter

One-Pot Oxidative Cleavage of Olefins to Synthesize Carboxylic Acids by a Telescoped Ozonolysis–Oxidation Process

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Abstract A mild one-pot ozonolysis-oxidation process of alkenes to synthesize carboxylic acids is described. Conducting the ozonolysis in an aqueous organic solvent eliminates secondary ozonide formation and the intermediates generated are readily converted into a carboxylic acid by adding sodium chlorite. Following a reductive quench, the desired acids are isolated in high purity and high yield by simple extraction.

Key words ozonolysis, carboxylic acids, green chemistry, alkenes, oxidation

The oxidative cleavage of olefins by ozone is an efficient and environmentally sustainable method to generate oxygenated compounds.¹ Olefin ozonolysis is commonly used to prepare aldehydes, ketones, and alcohols through formation of a secondary ozonide followed by an in situ degradation with a reducing agent.² A direct conversion of olefins to esters by an ozonolysis has also been studied.³ When the final target is a carboxylic acid, a two-step process is employed where, after reduction of the ozonide, the isolated aldehyde is oxidized in a separate step.⁴ In other instances, the carboxylic acid can be generated post ozonolysis by the addition of hydrogen peroxide; however, only a limited number of procedures document this process.⁵ An alternative to ozone, metal-catalyzed oxidative cleavage of olefins with stoichiometric oxidant, also generate carboxylic acids in a one-pot procedure.⁶ Unfortunately, these catalysts are often costly and are difficult to remove which is further exacerbated when used as the final synthetic step of an active pharmaceutical ingredient (API). As part of our design of an efficient and scalable process to an API, we sought a metalfree, one-pot ozonolysis-oxidation reaction of an olefin to synthesize carboxylic acids.

In the widely accepted mechanism (Scheme 1), ozone reacts with an alkene by a 1,3-dipolar addition to generate the primary ozonide 2 which rapidly undergoes a retrocyclization to a mixture of carbonyl and carbonyl oxide intermediates **3**.⁷ These intermediates quickly recombine in aprotic solvents to form the secondary ozonide 4 which is subsequently reduced to aldehydes, ketones, or alcohols. In the past decade, a number of techniques have been developed to address the potential hazards of ozonolysis reactions,⁸ namely managing the formation of high-energy intermediates and the control of the exothermic nature of the reaction. Of utmost concern, secondary ozonides 4 have a high energy of decomposition and yet, they often react slowly by reaction workup.⁹ The combination of high energy and slow reactivity gives way to their explosive nature.¹⁰ One method to minimize the accumulation of these intermediates and increase the safety of the process is by running the ozonolysis in a continuous manner.¹¹



Scheme 1 Ozonolyis reaction pathway in aprotic solvents

Additives and solvent choice in the ozonolysis reaction have been used to avoid secondary ozonide formation. The addition of protic solvents, such as methanol (Scheme 2, eq. 1), result in the formation of methyl peroxy acetals **5** in lieu

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of the secondary ozonide by intercepting intermediate **3**. The methyl peroxy acetals are typically reduced to the corresponding carbonyl or alcohol but in some instances, they can be isolated.¹² Catalytic pyridine also suppresses ozonide formation at cryogenic temperatures, and the aldehyde can be isolated without a reductive workup (Scheme 2, eq. 2).¹³ By conducting an ozonolysis reaction in an aqueous/organic solvent mixture (Scheme 2, eq. 3), Dussault found the aldehyde product could be isolated without a reductive quench by way of a hydroperoxy acetal intermediate 6. In addition, the ozonolysis could be conducted at 0 °C instead of using crvogenic conditions (Scheme 2, eq. 3).¹⁴ We conceived an ozonolysis method in which, utilizing an aqueous solvent, the short-lived intermediate 6 formed at noncryogenic temperatures could be intercepted with a second oxidant to form a carboxylic acid in one pot.



Scheme 2 Ozonolysis conditions which avoid secondary ozonide formation

We began by replicating the ozonolysis conditions developed by Dussault using 4-phenylbutene (**7**) in 10 volumes of 5% water-acetonitrile at 0 °C.¹⁵ Ozone was delivered to the reaction with a subsurface sparger while sweeping the reactor headspace with nitrogen.¹⁶ In addition to an ice bath, the exothermicity of the reaction was controlled by the rate of ozone delivery. Diluting the reaction from 10 volumes to 20 volumes of solvent also permitted the heat to dissipate more readily.¹⁷ In the 5% aqueous system a small quantity of the secondary ozonide (2 area%) was formed; however, no evidence for the secondary ozonide was found upon increasing the solvent water content to 10% (<1 area%).¹⁸ In lieu of using a chemical indicator to determine the ozonolysis reaction endpoint,¹⁹ the head space of the reactor was monitored for ozone.²⁰

Once the ozonolysis was complete, the reaction composition was analyzed to help determine a plausible method to produce the desired carboxylic acid in situ (Scheme 3). A mixture of aldehyde, peroxyacetal, and hydrate intermediates **8** were observed to be in equilibrium²¹ and the solution tested positive for peroxides. Unexpectedly, the solution had a pH value of ca. 1. This drop in pH was not solely due to the ozonolysis of the substrate as a decrease of the pH value was measured when a 10% water-acetonitrile solution was ozonolyzed in the absence of an alkene.²²



Scheme 3 Ozonolysis reaction mixture in 10% H₂O–MeCN

The observation that the end of reaction was acidic informed our selection of sodium chlorite as a second oxidant. Sodium chlorite acts as a mild oxidizing agent in aqueous media at a pH < 4 converting aldehydes into carboxylic acids (Pinnick oxidation).²³ Given the high concentration of aldehyde in equilibrium with the other ozolysis products, the mixture should all convert into the carboxylic acid in the presence of sodium chlorite. Though the Pinnick oxidation is traditionally carried out in THF–*t*-BuOH solvents with a phosphate buffer and a hypochlorite scavenger, acetonitrile and hydrogen peroxide have been successfully used as solvent and scavenger, respectively.²⁴

A 2 M sodium chlorite solution was added to the ozonolysis end-of-reaction solution in one equivalent, increments monitoring for carboxylic acid formation (Table 1). Gratifyingly, after the first equivalent was added and aged for one hour, acid 9 was produced in 34%. Slow delivery of the chlorite solution to the reaction mixture was required to control the exothermicity of the oxidation reaction. A second equivalent of sodium chlorite was added, aged, and the mixture further converted into acid 9, however, the reaction appeared to stall at 60%. A third equivalent of sodium chlorite appeared to have little impact after aging for an hour; however,²⁵ aging the reaction overnight following addition of a fourth equivalent of sodium chlorite resulted in the full conversion into carboxylic acid 9. The excess amount of oxidant required is most likely due to the chlorite decomposition in the presence of reaction byproducts.26

Prior to isolation of acid **9**, a reductive workup was necessary to safely quench any residual oxidants such as chlorite, hypochlorite, and hydrogen peroxide. The reaction was quenched with a 2 M sodium bisulfite solution; a mildly exothermic reaction. The temperature rise was controlled by the addition rate. The reaction mixture remained yellow until approx 3.5 equivalents of the solution was added. A total of four equivalents of sodium bisulfite was required before the reaction mixture tested negative for oxidants. Af-

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 Table 1
 Ozonolysis End-of-Reaction Solution Reacting with Sodium

 Chlorite



1 12 1 34	$NaClO_2$ (equiv)	T _{int} rise (°C)	lime aged (h)	9 (area%)	
	1	12	1	34	
2 8 1 60	2	8	1	60	
3 4 1 67	3	4	1	67	
4 1 16 100	4	1	16	100	

ter a simple extraction, 3-phenylpropanoic acid **9** was isolated in 96% yield and >95% purity by ¹H NMR.

With the data collected from these experiments, a general one-pot ozonolysis-oxidation procedure was developed to synthesize carboxylic acids. In a typical experiment the primary alkene in 20 volumes of 10% water-acetonitrile is subjected to ozone at 0 °C. Once ozone is detected in the reaction head space, the ozonolysis is stopped. An aqueous solution of sodium chlorite (2 M, 4 equiv) is added to the reaction at a rate adequate to maintain the internal reaction temperature <15 °C, and the reaction is stirred at ambient temperatures for >12 hours. The end-of-reaction mixture is quenched with sodium bisulfite (2 M, 4 equiv) at a rate such that the internal temperature is <35 °C. Following quench, the product is isolated by extraction.²⁷

The generality of this process was evaluated with a variety of primary alkenes (Table 2). Benzoic acids with either electron-rich or electron-poor substituents were readily synthesized from the corresponding styrenes (Table 2, entries 2–4). 4-Vinylpyridine was an adequate substrate providing isonicotinic acid albeit in moderate yield (Table 2, entry 5). Unfunctionalized and acetylated monoalkylalkenes (Table 2, entries 6 and 7) were smoothly transformed into their corresponding carboxylic acids as well as the unprotected alcohol in 7-octene-1-ol (Table 2, entry 8). N-Allyl benzamide (Table 2, entry 9) was converted into the corresponding acid using these conditions which exemplifies a new method to generate amino acids.

In summary, a mild, one-pot, and metal-free process to oxidatively cleave alkenes to carboxylic acids has been developed. By utilizing an ozonolysis in aqueous solvent, the olefin is cleaved, thereby avoiding high-energy intermediates under noncryogenic conditions. These intermediates are further oxidized with sodium chlorite to produce the desired carboxylic acid. Because this process contains no





^b Assay yield.

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heavy metals, pure products are isolated by a simple extraction. To further exemplify the safety and utility of this process, a carboxylic acid API was safely manufactured on >20 kg of an alkene (>40 mol) in high yield and purity. This process will be detailed in a future publication.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560659.

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- (15) Though the conditions reported use 5% H_2O -acetone, it notes that MeCN is an adequate organic solvent.
- (16) **Caution**: In addition to ozone's inherent toxicity, bubbling ozone/oxygen into a flammable organic solvent poses a fire hazard.
- (17) Solutions of heavier substrates (>500 g/mol) are inherently more dilute in 20 volumes (mL/g) of solvent and are less exothermic during the ozonolysis allowing the reaction to be conducted at r.t.
- (18) Secondary ozonide formation was measured by LC-MS, see Supporting Information.
- (19) Unlike some solvent systems, 10% H₂O–MeCN does not turn blue when saturated with ozone. Chemical indicators such as Sudan III can also be used to determine the reaction end point. See: Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. Synthesis **1980**, 807.
- (20) An EcoZone model EZ-1X ozone detector was positioned at the reactor outlet. During the ozonolysis, no ozone was detected in the head space until the alkene was consumed. This result was repeatable with all substrates assuming a slow ozone delivery rate (<2 scfh [standard cubic feet per hour]).</p>
- (21) In a number of substrates the peroxyacetals were detected by LC–MS. Repeated injections of the sample showed the slow conversion of the peroxyacetals to the aldehyde/hydrate over time.
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- (25) Aging the reaction overnight with 3 equiv of sodium chlorite resulted in 90–95% conversion.
- (26) It is known that NaClO₂ can be reduced with hypochlorite ions and with hydrogen peroxide in acidic media. An additional gaseous byproduct was formed detectable by the yellow color of the nitrogen bubbler oil. The exact identity of this gas is not known but is presumed to be Cl_2 or ClO_2 , see ref. 23.
- (27) Representative Ozonolysis-Oxidation Procedure: Formation of 3-Phenylpropanoic Acid (Table 1, Entry 1) To a vial was added a solution of 4-phenyl-1-butene (1 mL, 0.88 g, 6.66 mmol, 1 equiv) dissolved in MeCN (15.8 mL, 18 mL/g) and H₂O (1.8 mL, 2 mL/g). The solution was cooled to 0 °C and sparged with ozone at a rate of <2 scfh (standard cubic feet per hour) while purging the head space of the vial with nitrogen. Once ozone was detected in the head space, the ozone was stopped and reaction completeness was confirmed by LC-MS. A magnetic stir bar was added to the vial and the solution stirred rapidly. An aqueous solution of NaClO₂ (80 wt%, 3.01 g, 26.6 mmol, 4 equiv) in H₂O (14 mL) was added portionwise to the reaction while maintaining a internal reaction temp <15 °C. The cold bath was removed from the reaction and the mixture stirred for >12 h at r.t. under 1 atm of nitrogen. A solution of NaHSO₃ was made by dissolving Na₂S₂O₅ (2.77 g, 14.58 mmol, 2.19 equiv) in H₂O (14 mL). This solution was slowly added to the reaction maintaining a internal temperature <35 °C and the mixture stirred for 10 min. EtOAc (10 mL) was added to the mixture, and the layers were separated. The aqueous layer was extracted with EtOAc, the organic layers combined, dried over MgSO4, filtered, and concentrated to provide a colorless oil (0.95 g, 95% yield). 1H NMR (400 MHz, CDCl3): $\delta = 2.71$ (t, J = 8.0 Hz, 2 H), 2.96 (t, J = 8.0 Hz, 2 H) 7.18-7.32 (m, 5 H), 10.30-11.30 (br s, 1 H).