The Breadth of Ozonolysis Including Industrial Reactions

INTRODUCTION

The oxidation of organic compounds to new entities via ozonolysis offers tremendous benefits over alternative environmentally unfriendly technologies. Unbeknown to most, ozonolysis is also economical and can achieve the desired compound by alternative oxidation technologies. Unfortunately, most chemists at the discovery and route selection stages of new molecular entities are unaware of the ability to scale up this reaction. Historically, ozonolysis has been used in structural determination prior to the advent of modern spectroscopic methods. In addition to correcting the notion that the reaction cannot be conducted at scale, this article shows the breadth of possible ozonolysis substrates which not only includes alkenes, but also a number of other substrates.

Ozone was discovered in 1840 by Schönbein. Later in 1847, it was found that alkenes could be cleaved by ozone. Ozonolysis has proved to be a convenient and highly effective method of oxidatively cleaving a double bond, which can lead to a wide array of potential products. Alkenes are by far the most common type of substrates utilized in this reaction (1). The mechanism was first proposed by Crigee in 1953. The initial addition proceeds after a 1,3 cycloaddition to form an unstable malaonozide (1, 2), that then rearranges to form the more stable ozonide shown in Scheme 1. The wide variety of reductants and oxidants that can be used in the reaction work-up procedure allows the formation of a variety of products and displays the versatility of this reaction. Aldehydes can be produced by catalytic hydrogenation over palladium on carbon (3), platinum oxide (4), triphenylphosphine (5), dimethyl sulfoxide (6), Raney nickel (7) and by reduction with zinc in acetic acid (8). The conversion to alcohols can be accomplished using reducing agents such as sodium borohydride (9) or lithium aluminium hydride (10). Cleavage of the ozonide to carboxylic acids can be performed using hydrogen peroxide (11), formic acid and acetic acid (3, 12-14). The reaction conditions for ozonolysis are mild and display a high level of selectivity and yield. For chemical efficiency there are few reactions that match ozonolysis with sixty six percent of the molecular mass of ozone incorporated into the final products. This avoids the use of alternative oxidants, such as permanganate, periodic acid and peroxide with the latter often requiring heavy metals, making ozonolysis a much cleaner and environmentally friendly process. In addition, ozone can eliminate additional reactions that may be required to obtain the correct substrate. Although ozonides are unstable many have been isolated often, by allowing a low boiling solvent to evaporate. The ozonide of isobutylene has been isolated as has the ozonide of 1-pentene by distillation at 43 °C and reduced pressure (1). Additional stability is achieved with electron withdrawing groups in the alpha position.

INDUSTRIAL CONSIDERATIONS

Only a handful of companies offer ozonolysis at an industrial scale capable of producing many hundreds of metric tonnes of material annually. For example, Uquifa has the capability to produce over 300 Kg’s per day of ozone. The ozone generated is directly fed to one of two specialized 8 or 10 M³ reactors that can achieve greater than -100 °C with high mass transfer rates. Ozone is generated from oxygen by treatment via an electrical discharge with a potential drop of 11,000 to 15,000 Volts. With ozone’s inherent strong oxidizing capability, toxicity and corrosive properties specialized equipment is required. A number of
compounds as well as active pharmaceuticals have been manufactured, which include cephalosporin, acetomycin, 2-hydroxyindan-2-carboxaldehyde and glyoxal synthesized from benzene.

**BREADTH OF OZONOLYSIS**

As mentioned above, oxidation with ozone is not limited to alkenes. Among the additional substrates ozone reacts with are acetals (15), aldehydes (16), aromatic compounds (17), azides (18), ethers (19), glycosides (15), hydrazones (20), \( \alpha \)-ketocyanophosphoranes (21), oximes (20), nitro compounds (22), organomercury compounds (23), phosphines (24), phosphites (24), selenium compounds, semicarbazones (20), sulphides (25) and tertiary alkanes (26). The synthesis of \( \alpha \)-hydroxyl carboxylic esters, which are an important class of compounds in natural product synthesis, can be greatly simplified by the use of ozonolysis. Typically these compounds have to be prepared by the zinc-mediated Reformatsky reaction or the Mukaiyama silyl ketone reaction. These routes require the protection of functional groups, such as hydroxy groups. Yi et al. have developed an effective route to \( \alpha \)-hydroxy carboxylic esters with the ozonolysis of \( \alpha \)-hydroxy alkenes (27). As the reaction is conducted in an alcoholic solvent, a variety of esters can be produced. A racemic switch is desired for ibuprofen which is currently manufactured at scale providing both the (S) and (R) enantiomers. The (S) enantiomer is significantly more active hence, there is a desire to find an alternative synthetic pathway. Acemoglu developed a novel route where an alkenyl sulphone is converted by ozonolysis and borohydride reduction to the sulphonyl alcohol (28). Removal of the sulphones followed by oxidation led to enantiomerically enriched (S)-Ibuprofen.

An example of an ozonolysis reaction at industrial scale is Pfizer’s synthesis of 2-hydroxyindan-2-carboxaldehyde (29). The compound is prepared from 2-indanone by reaction with vinylmagnesium bromide, and the resulting alkene was subjected to ozonolysis. The product, 2-
The selective nature of ozonation is shown in the synthesis of artemisinin. In this reaction sequence (Scheme 2) two ozonolysis steps can be performed separately allowing for the isolation of the novel carbonyl/carbonyl substituted vinylsilane (30). The synthesis is completed by a second ozonolysis followed by an acidification step, which closes the oxygen containing ring structure and produces the required compound. The vinylsilane can be transformed with a number of reactions prior to the final ozonolysis step leading to analogues of artemisinin.

The scope of ozonolysis goes beyond alkenes. In the synthesis of Kumaussale, a marine acetogenin, a pivotal reaction was the conversion of a selenium derivative to a nitronate (+Scheme 2) [48]. In situ treatment of this salt with ozone followed by reduction of the ozonide with dimethyl sulphide directly transformed with a number of reactions prior to the final ozonolysis step leading to analogues of artemisinin.

These intermediates have been used in the synthesis of a large number of natural products. Further, many pharmaceutical intermediates and active pharmaceuticals have been synthesized at scale. It is to be hoped that more development chemists will recognize the atom efficiency, breadth, selectivity, greener technology and that multi-tonne manufacture is indeed possible. Additional information may be found on www.ozonation.com and in the following reviews (37-39).

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REFERENCES AND NOTES

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