

Ozone as an Oxygen Source for Alkene Ene-Reactions

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Summary. A strategy was developed which uses the adduct of ozone and triphenyl phosphite as a substitute for photochemically generated singlet oxygen in ene reactions of olefins. The resulting allylic hydroperoxide can be conveniently reduced by a second mole of phosphite to yield the corresponding allylic alcohol. The aryl phosphate produced as the by-product can either be recycled by reduction or used itself as a commodity. As an example, the two key steps of the rose oxide synthesis involving singlet oxygen can thus be reduced to a one pot procedure. With respect to the reaction mechanism, additional arguments for the direct reaction of the olefin with the phosphite ozonide were gathered. A simple decomposition of the ozonide to produce singlet oxygen was made rather unlikely.

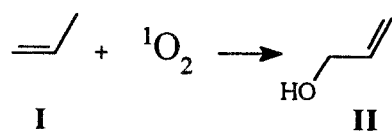
Keywords. Ene reaction; Phosphite ozonide; Organic phosphate; Rose oxide.

Ozon als Sauerstoffquelle für En-Reaktionen von Olefinen

Zusammenfassung. Es wurde eine Strategie zum Ersatz von photochemisch erzeugtem Singlett-Sauerstoff durch das Addukt aus Ozon und Triphenylphosphit zum Einsatz in En-Reaktionen von Olefinen entwickelt. Das entstehende allylische Hydroperoxid kann durch ein zweites Molekül Phosphit einfach zum entsprechenden allylischen Alkohol reduziert werden. Das als Nebenprodukt entstehende Arylphosphat kann entweder durch Reduktion recycelt oder direkt als Handelsware weiterverwendet werden. Auf diese Weise können zum Beispiel die beiden Stufen der Rosenoxidsynthese, an denen Singlett-Sauerstoff beteiligt ist, zu einer Eintopfreaktion vereinfacht werden. Bezüglich des Reaktionsmechanismus wurden zusätzliche Hinweise auf die direkte Reaktion des Phosphitozonids mit dem Olefin gefunden. Eine Zersetzung des Ozonids unter Bildung von Singlettsauerstoff ist nicht wahrscheinlich.

Introduction

The ene-reaction of alkenes (I) with singlet oxygen provides a valuable method to derivatize these compounds into allylic alcohols (II) *via* the corresponding hydroperoxides (Scheme 1) [1]. Even products of commercial importance are dependent on this reaction step [2, 3].



Scheme 1

However, the necessity to use singlet oxygen for this transformation renders this otherwise elegant step cumbersome. Singlet oxygen is commonly produced photochemically [1]. As a consequence, rather long reaction times and problems with running large scale photo reactors are encountered [3]. The energy input is high and the overall efficiency rather low. Therefore, alternative procedures to achieve this goal would be of interest.

Ozone on the other hand can be produced easily, and even technical applications pose no serious problems [4]. Thus, using oxygen atoms of an ozone molecule within the scheme of an ene-reaction was thought to be an interesting strategy. However, the ecological aspect of using this reagent together with activating catalysts had to be kept in mind, because in the case of photochemically produced singlet oxygen there are virtually no problematic by-products which could interfere with the environment.

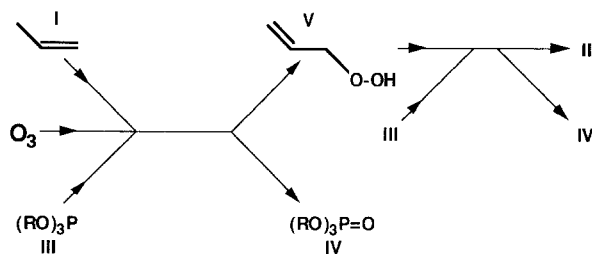
Since it is known that singlet oxygen is also produced by chemical reactions, especially in the decomposition reaction of phosphite ozonides [5], it seemed to be promising to investigate this possibility.

Results and Discussion

Synthetic Aspects

A variety of alkyl and aryl phosphites are known to yield ozone adducts of different stability. Whereas simple alkyl phosphite ozonides decompose at temperatures below -80°C into the corresponding phosphates and singlet oxygen, aromatic derivatives tend to be more stable, usually up to -30°C [5]. The most stable ones (up to room temperature) are observed in the case when the phosphite phosphorous atom is located within a cyclic substructure [6].

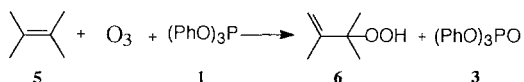
To use such phosphites as oxygen transfer agents from ozone to an olefin, the strategy given in Scheme 2 was devised. Accordingly, by using the phosphite **III** in the reaction with ozone and the olefin **I**, the corresponding phosphate **IV** will be obtained together with the derivatized product precursor, the hydroperoxide **V**. The latter can then be reduced to the desired allylic alcohol **II**. This can be achieved either by conventional reducing agents like sodium sulfite, or more conveniently in this case, by means of a second mole of the phosphite **III**, which produces another mole of the phosphate **IV**.



Scheme 2

The nature of a certain phosphite **III** is constrained with respect to reactivity and environmental problems. First, the ozone adduct has to be sufficiently stable. Secondly, to recycle **IV** into **III**, a convenient reduction method has to be available. Alternatively, a possibility to use the phosphate **IV** itself as a secondary product might be interesting. These criteria are met by triphenyl phosphite (**1**), or even better, by tricresyl phosphite (**2**). The ozone adducts of **1** and **2** are stable up to -30°C . Triphenyl phosphate (**3**) might be conveniently reduced [7], and the reaction product from **2** is tricresyl phosphate (**4**). The latter is a commercial commodity and is used as softener for PVC and nitrocellulose or as an additive to lubricants.

To explore the optimal conditions of Scheme 2, the reaction of tetramethylethylene (**5**) with ozone in the presence of **1** was studied (Scheme 3). First of all, it was observed that the yield of the corresponding hydroperoxide **6** was strongly dependent on the reaction temperature. This is illustrated in Fig. 1. Higher temperatures than -50°C resulted in severely lowered yields. This effect is thought to be due to the increasing dissociation of the phosphit ozonide at higher temperature. The singlet oxygen thus obtained at rather low concentrations would escape partly from the reaction mixture and could therefore react with the olefin only to a small extent, diminishing the overall yield.



Scheme 3

With respect to other solvents, dichloromethane and acetone gave comparable results. However, protic solvents (like methanol) resulted in dramatically reduced yields. The absolute concentration of phosphite **1** in the reaction mixture also showed an optimum yield (83%) in the range of 0.25 mol/l. In more dilute solutions

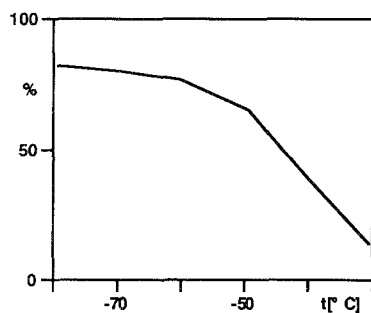


Fig. 1. Temperature dependent yield (% of theoretical yield) of the hydroperoxide **6** from the equimolar reaction of olefin **5** with the ozonide of **1** in dichloromethane as the solvent

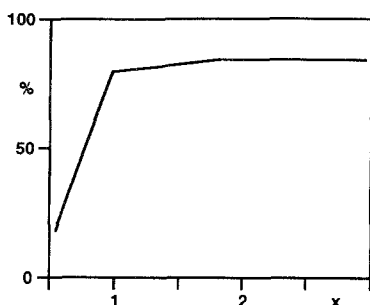


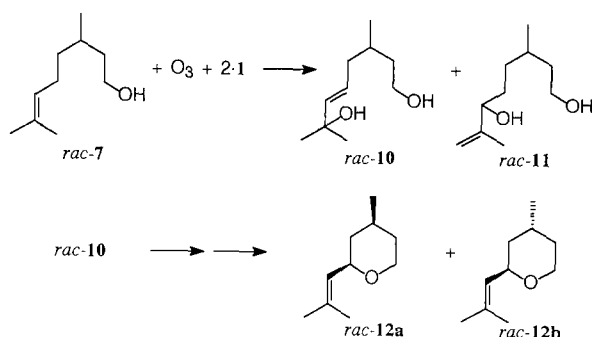
Fig. 2. Dependence of the yield (% of theoretical yield) of the hydroperoxide **6** on the molar ratio of **1** to olefin **5** (x) in dichloromethane as the solvent at -80°C

the yield was very low (*e.g.* at 0.05 mol/l: 40%), whereas at higher concentrations only a small reduction in yield was observed (*e.g.* at 1 mol/l: 75%).

The optimum yield was obtained at a molar ratio of 1.0 between phosphite **1** and olefin **5** as shown in Fig. 2. This result clearly demonstrates the formation of the phosphite ozonide in the course of the reaction.

An Example: The Rose Oxides

The key steps in the synthesis of the valuable perfumery ingredient, *cis* and *trans* rose oxide, is the reaction of citronellol (**7**) with photochemically generated singlet oxygen to yield 3,7-dimethyl-7-hydroperoxy-5-octen-1-ol (**8**) and 3,7-dimethyl-6-hydroperoxy-7-octen-1-ol (**9**) [8]. These hydroperoxides are then reduced with sodium bisulfite [9] to yield 3,7-dimethyl-5-octen-1,7-diol (**10**) and 3,7-dimethyl-7-octen-1,6-diol (**11**) in good yield and a ratio of **10**:**11** = 2:1. Acid catalyzed rearrangement and dehydration of **10** then yields the *cis* and *trans* rose oxides [10]. Since **11** does not interfere with this reaction, there is no need to separate the diol mixture (Scheme 4) [8].



Scheme 4

These two steps could be simplified into a one pot procedure using the strategy developed above. According to Scheme 2, *rac*-7 was reacted with equimolar amounts of the ozone adduct of **1** in dichloromethane at -80°C . To reduce the hydroperoxides *rac*-8 and *rac*-9, a second molar amount of phosphite was then added, and after work up the desired diols *rac*-10 and *rac*-11 were obtained in an overall yield of 56% and in a ratio of **10**:**11** = 2:3. As discussed above, *rac*-10 could then be converted to the rose oxides (*rac*-12a, *rac*-12b, with the *cis* diastereomer *rac*-12a predominating) following the procedure described in literature [8, 10]. The reaction was very smooth and could be executed within a very short period (about 2 h) as compared to the photochemical step. This example of the rose oxides demonstrates that ozone can easily serve as an oxygen source for ene reactions, avoiding the problems associated with photochemical steps.

Mechanistic Aspects

There is broad discussion in literature about the mechanistic details of the reaction between phosphite ozonides and olefins. Two strongly different mechanisms may be elaborated. In the first one, the phosphite ozonide decomposes into

phosphate liberating singlet oxygen. The latter then reacts with the olefin in the ene reaction to yield the corresponding hydroperoxide. This mechanism was invoked from the experimental fact that phosphite ozonides decompose on warming [5]. The second mechanism involves the direct reaction between the phosphite ozonide and the olefin to yield the phosphate and the hydroperoxide. This latter mechanism is favored by experiments showing that certain olefins which react smoothly with singlet oxygen don't so with phosphite ozonides [11]. Moreover, the product distributions obtained with singlet oxygen are dissimilar to the ones obtained using phosphite ozonides [12], and the reaction proceeds also in the presence of singlet oxygen quenchers [13].

Two further examples were found which also favor the second mechanism. First, cyclohexene did not react with triphenyl phosphite ozonide under conditions in which singlet oxygen produces the corresponding cyclohexene-3-hydroperoxide [1]. Second, furan-2-aldehyde which is known to react with singlet oxygen [14] to yield 5-hydroxy-3-butenolide did not react with triphenyl phosphite ozonide. From the experiment contained in Fig. 1 one could deduce that the reaction proceeded best at a temperature at which the ozone adduct was perfectly stable, thus again favoring the mechanism of the direct reaction between complex and olefin. Finally, the latter mechanism was also corroborated by the finding that the olefin was optimally attacked in the case of equimolar amounts of olefin and added phosphite as illustrated in Fig. 2.

Experimental

NMR spectra (CDCl_3) were run on the Bruker AC 200 spectrometer with TMS as internal standard. Ozone was generated from pure oxygen (20l/h) using a Labor-Ozonisator-301 of E. Sander Elektroapparatebau at 5.5 kV. Triphenyl phosphite, *rac*- β -citronellol, furfural, cyclohexene, and tetramethylethylene were of commercial origin (Merck, Aldrich). *p*-Tricresyl phosphite was prepared according to [15].

Preparation of phosphite ozonide solutions

5 mmol phosphite was dissolved in 25 ml CH_2Cl_2 and cooled to -80°C . Through this thermostatted solution an ozone/ O_2 stream was bubbled until the solution became blue due to free ozone (about 12 min.). The solution was then purged with argon until the blue color disappeared and the gas at the outlet did not color a ZnJ_2 -starch reagent paper.

Reactions of phosphite ozonides with olefins

To 5 mmol ozonide in 25 ml CH_2Cl_2 at -80°C , a precooled solution of 5 mmol of the olefin dissolved in 5 ml CH_2Cl_2 was added dropwise under an argon atmosphere. The reaction mixture was then brought to the specified reaction temperature and kept there for 30 min.

Workup of the reaction mixtures

The solvent was evaporated *in vacuo* and the hydroperoxide yield determined either by ^1H NMR in CDCl_3 solutions, by chromatography (SiO_2 -gel-60, solvent: petrolether/diethylether = 4/1), or by bulb-to-bulb distillation at reduced pressure.

Reduction of hydroperoxides

To the reaction mixture a solution of 5 mmol triaryl phosphite in 20 ml CH₂Cl₂ was added under agitation by argon bubbling at the reaction temperature. Then the stirred solution was brought to room temperature and kept there for 2 h; workup as given above.

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