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Activation of Aqueous Hydrogen Peroxide for Non-Catalyzed Dihydroperoxidation of Ketones by Azeotropic Removal of Water

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Cyclic and acyclic ketones were selectively converted to *gem*-dihydroperoxides in 72-99% yield with 30% aq. hydrogen peroxide by azeotropic distillation of water from the reaction mixture without any catalyst. The reactions were more selective as with 100% H_2O_2 and due to neutral conditions also less stable products could be obtained.

Natural products containing peroxide or hydroperoxide groups exhibit broad-spectrum bioactivity but they have not been fully exploited as therapeutic agents due to their low availability.[1] The discovery, that naturally occurring sesquiterpene endoperoxide artemisinin (from *Artemisia annua*) is active also against chloroquine-resistant strains of the malaria parasite, has heightened interest in organic peroxides as bioactive compounds.[2] Besides being recommended as a first-line treatment for malaria for over a decade, artemisinin and its derivatives have a potential to be used as antitumor, antiviral, antibacterial and anti-inflammatory agents therapies.[3] Simplification of the artemisinin structure was necessary to facilitate both its production and to improve its pharmacokinetic properties. This resulted in the development of various synthetic peroxides, of which the 1,2,4,5-tetraoxanes are the easiest to synthesize and contain two peroxide groups.[4] Synthesis of symmetrical 1,2,4,5-tetraoxane is achieved by acid-catalysed peroxidation of a ketone with hydrogen peroxide.[5] Unsymmetrical tetraoxanes, being more diverse structurally, can only be prepared using a two-step procedure involving two different ketones via the formation of *gem*-dihydroperoxides (DHP) as intermediate products.[6] A one-pot procedure was also reported.[7] This makes DHPs an interesting starting precursor for the preparation of this biologically important class of peroxides.

Various methods for the synthesis of DHPs have been developed.[8] The classical approach involves the ozonolysis of ketals, alkenes or enol ethers in the presence of hydrogen peroxide in diethyl ether. The yields are usually low due to weak selectivity and the formation of several peroxidic compounds. Direct peroxidation of carbonyl compounds with H_2O_2 would be favourable but the reaction is non-selective and the product when using cyclohexanone was named as a cyclohexanone-hydrogen peroxide complex.[9] To increase selectivity researchers have turned towards using catalysed processes *i.e.* acids,[10] metal complexes,[11] iodine,[12] and fluorinated alcohols,[7a, 13] to prepare DHPs. Oxygen has also been used to generate DHPs photochemically.[14]

In 2010, Itoh and co-workers were the first to publish a non-catalysed synthesis of DHP using 5 equivalents of 35% aq. H_2O_2 in dimethoxyethane (DME).[15] In our study on iodine-catalyzed dihydroperoxidation published in 2008 we also performed a blank experiment but found that reaction did not occur.[12] This dichotomy could point to our lack of knowledge about the hydroperoxidation of ketones. Based on this finding we decided to investigate the activation of hydrogen peroxide for the hydroperoxidation of ketones to see how the selective formation of dihydroperoxides, which are precursors of bioactive non-symmetrical 1,2,4,5-tetraoxanes, could be achieved under non-catalysed conditions.

We initially followed the method as reported in the literature for non-catalyzed dihydroperoxidation using 4-methylcyclohexanone **1a** as a model substrate.[15] A mixture of ketone **1a** and 5 equiv. of 30% H_2O_2 in acetonitrile was stirred for 10 hours at room temperature. The reaction mixture was then concentrated under reduced pressure and purified using column chromatography. This resulted in the isolation of dihydroperoxide **2a** as the main product (Scheme 1, path A). To clarify at which step of the procedure H_2O_2 becomes activated allowing the conversion of **1a** to DHP **1b** we substituted the work-up procedure for the biphasic isolation procedure as in the iodine-catalysed method; the reaction

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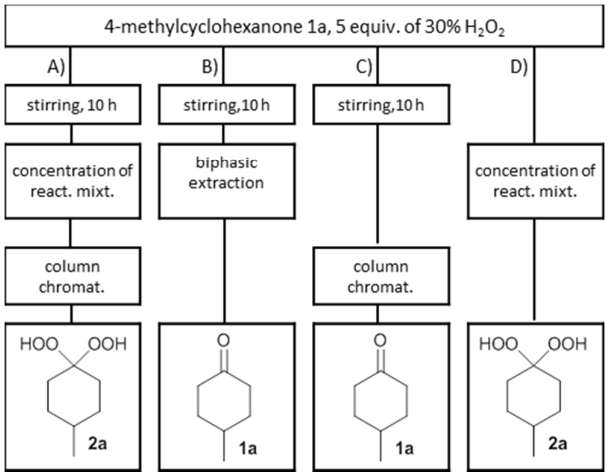
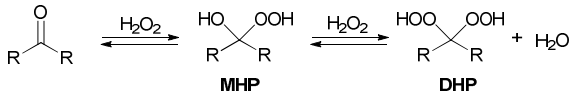
mixture was diluted with dichloromethane, washed with water to remove excess H_2O_2, dried and the organic solvent evaporated.[12a] After purification by column chromatography only the ketone was isolated (Scheme 1, path B) proving that dihydroperoxidation does not occur during the "reaction step". An alternative explanation would be that the mild acidity of the silica gel triggers the activation of the H_2O_2. To test this, the reaction mixture was placed directly onto the column without prior concentration (Scheme 1, path C). Again only the ketone **1a** was obtained. Since activation did not occur either during stirring (10 h) or during chromatography, the only possibility left is that activation occurs while concentrating the reaction mixture under reduced pressure. For this reason, ketone **1a** and 5 equiv. of H_2O_2 were dissolved in acetonitrile and concentrated without having been previously stirred (Scheme 1, path D). After purification, dihydroperoxide **2a** was isolated as the major product.



Scheme 1 Various isolation procedures in reaction of 4-methylcyclohexanone 1a and 5 equiv. of 30% H_2O_2

Clearly, aqueous solution of H_2O_2 becomes activated during the evaporation of the solvent. The first step would be addition of H_2O_2 to carbonyl group forming unstable perketal MHP that is in equilibrium with starting ketone (Scheme 2). While the second step of reaction is acid-catalyzed one and could lead to DHP and to other peroxidic products. It was found out that the equilibrium constant for addition of H_2O_2 to carbonyl group is higher than that of water.[16] Since acetonitrile forms an azeotrope with water, it would influence the second step by removing the water from the reaction mixture. The question arises to whether or not activation is a result of classical concentration or the decreasing amount of water in the reaction mixture.



Scheme 2 Reaction of ketone and hydrogen peroxide

Another important question is how evaporation affects the course of hydroperoxidation as it is well known that several types of reactions are accelerated by immediate evaporation of solvent due to enhancement of molecule-to-molecule contacts.[17] To elucidate those important questions we compared the reactivity of 30% and 100% H_2O_2 in MeCN, solventless reaction and after azeotropic removal of water in dihydroperoxidation reaction of two ketones: 2-methylcylcohexanone **1b** and 2-nonanone **1c**.

Thirty per cent hydrogen peroxide failed to convert 2-methylcylcohexanone **1b** within 45 min in either a MeCN solution or under solvent-free conditions and only after a prolonged reaction time did conversion occur with yields of 11% and 42%, respectively (Table 1). One hundred per cent of H_2O_2 was only slightly more reactive in MeCN solution, while in neat **1b** was converted in a 59% yield within 45 min but various peroxidic products were formed according to the NMR spectra. When ketone **1b** and 30% H_2O_2 were dissolved in MeCN and concentrated under reduced pressure, DHP **2b** was selectively formed (82% and 95% after 45 min and 24h, respectively). In a similar experiment using the less reactive 2-nonanone **2c**, a difference in reactivity when using 30% and 100% H_2O_2 was even more pronounced in neat, while in MeCN solution only trace amount of the product **2c** was formed (Table 1). Using a method of in situ concentration of 30% H_2O_2, the result was even better than with 100% H_2O_2 (68% and 85% yield, respectively). The method of in situ concentration of 30% H_2O_2 generates reactivity similar to using 100% H_2O_2, while selectivity is improved and does not require a catalyst.

Table 1 Conversion of ketones **1b** and **1c** to DHP **2b** and **2c** with different forms of H_2O_2 (4 equiv.)[a]

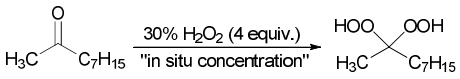
	t=45min	t=24h	t=24h
30% H_2O_2 / MeCN	0%	11%	0%
30% H_2O_2 / neat	0%	42%	0%
100% H_2O_2[b] / neat	59%[c]	75%[c]	68%
in situ concentration of H_2O_2[d]	82%	96%	85%

[a]Conversions of ketones were determined by ^{1}H NMR spectroscopy of the isolated reaction mixture as in Scheme 1B. [b]100% H_2O_2 was prepared by azeotropic distillation of 30% H_2O_2 in MeCN. [c]Mixture of peroxidic products. [d]10 mL of MeCN per mmol of ketone was added and concentrated under reduced pressure until solvent evaporated (20 min). A further 10 mL of solvent was then added and evaporated again. Reaction mixture was left standing at rt for 45 min and 24 h. 2.3 mL of MeCN would be theoretically needed to remove all the water by azeotropic distillation.

Our study of non-catalytic dihydroperoxidation continued by investigating the effect that the concentrating solvent has on the reaction. We assumed that any effect would be more pronounced when a less reactive ketone – 2-nonanone **1c** (Table 2) was used. Good DHP **2c** conversion rates were achieved in both a polar protic and aprotic solvent, and lower in a non-polar solvent. It appears that azeotrope formation is crucial for the conversion of the ketone into DHP, but it is not the only factor as indicated by low conversion in toluene. Polarity is also very important as indicated by the high

conversion in MeOH, albeit when the solvent forms an azeotrope with water conversion occurs more rapidly (87% in MeCN after 45 min and 12% in MeOH, respectively).

Table 2 The effect of solvent on the peroxidation of ketone **1c** by in situ concentration of H_2O_2[a]



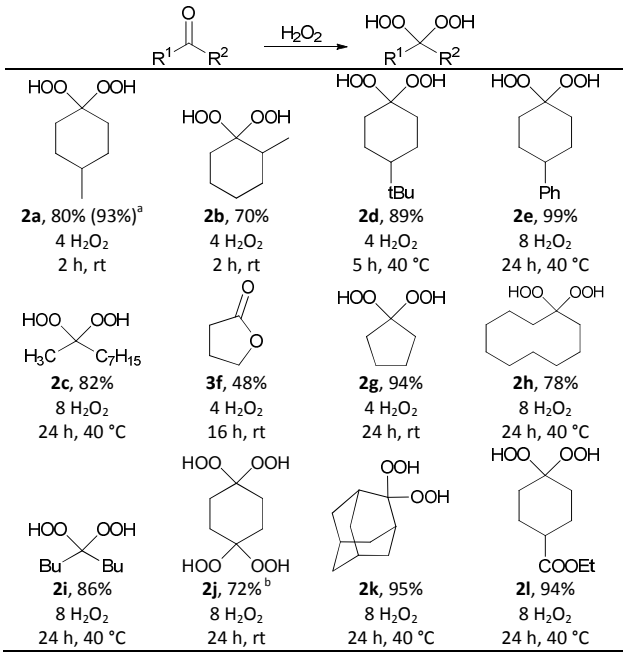
solvent (wt% of water in azeotrope)[b]	% DHP[c]
EtOH (4)	100
MeOH (0)	87
EtOAc (8.5)	85
MeCN (15.2)	85
DME (10)	51
DCM (1)	8
Et_2O (1.3)	28
hexane (5.6)	10
toluene (19)	14

[a]See Table 1, footnote d. [b]In parenthesis is the amount of water in the gas phase of the azeotrope (taken from: Smallwood, I M. Handbook of organic solvent properties, Butterworth-Heinemann: London, 1996, pp 302-303. Weast, R C. CRC Handbook of Chemistry and Physics, 55. ed., CRC Press: Cleaveland, and http://chemindustry.ru/Dimethoxyethane.php). [c]Conversions of ketones were determined by ^{1}H NMR spectroscopy of the isolated reaction mixture (as in Scheme 1B).

After initially studying which of the parameters activates the non-catalyzed peroxidation of ketones with 30% H_2O_2 during azeotropic evaporation, we applied this method to selected ketones to test its suitability for the synthesis of *gem*-dihydroperoxides (Table 3). Cyclohexanone derivatives **1a**, **1b**, **1d** and **1e** were converted to their corresponding DHPs **2a**, **2b**, **2d** and **2e** in good yields. Reactivity depended on the substituent and the reaction with liquid ketones **1a**, **1b** was complete within two hours at room temperature, while the solid ketones **1d**, **1e** required 40 °C and a prolonged reaction time for complete conversion. Nevertheless, yields were excellent – 89% and 99%, respectively.

The cyclic ketones **1g**, **1h**, **1k** were also converted using this method into their corresponding dihydroperoxides **2g**, **2h** and **2k** in good yields (78-95%). Alternatively, cyclobutanone **1f** underwent Baeyer-Villiger oxidation, even under neutral reaction conditions. Only in the case of the volatile starting ketone **1f-g**, 100% H_2O_2 was prepared before the reaction by azeotropic distillation of water by MeCN and the ketones were added subsequently and the mixture stirred for 16-24 h. As expected, the dihydroperoxidation of aliphatic ketones **2c** and **2i** was similar to the large cyclic ketone **1h** leading to the formation of DHPs **2c** and **2i** resulting in an 82% and 86% yield, respectively, and thus demonstrated that the position of the carbonyl group on the aliphatic scaffold does not fundamentally affect the reactivity of the ketones. The reactivity of 6-membered cyclic ketones functionalized at the position 4 was also studied. The 1,4-cyclohexanedione **1j** is very interesting due it having two carbonyl groups in the ring; dihydroperoxidation occurred on both the carbonyl groups quantitatively. Dihydroperoxide **2j** was not sufficiently stable to be purified by column chromatography and instead was purified by filtration to wash away excess H_2O_2. Ethyl 4-oxocyclohexanecarboxylate **1l** was converted into its corresponding dihydroperoxide **2l** and isolated with 94% yield.

Table 3. Synthesis of DHPs from ketones by in situ concentration of H_2O_2 in MeCN solution (yields refer to isolated products)[‡]



[a]10-mmol experiment.[§] [b]isolated by filtration.

Interactions between water and hydrogen peroxide reduces the reactivity of H_2O_2, hence the use of activators (metals, acids…). By using azeotropic distillation of water from the MeCN solution of 30% aq. H_2O_2 and starting ketone, activation occurs due to elimination of water with simultaneous peroxidation of carbonyl group. Although 100% H_2O_2 is a hazardous compound we have yet to observe any difficulties since the H_2O_2 is diluted, either by the solvent or by the precursor ketones. Activation is more pronounced in polar solvents which form azeotropic mixtures with water and various cyclic and acyclic ketones can be selectively converted to their corresponding DHPs. Neutral reaction conditions enable synthesis of less stable DHP. Cyclobutanone reacted only via a Bayer-Villiger oxidation to form lactone, even under neutral reaction conditions.

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Notes and references

‡Typical experiment: 1 mmol of ketone was dissolved in 10 ml of acetonitrile and then 4 or 8 mmol (453 mg or 906 mg) of 30% aqueous solution of H_2O_2 was added. The solution was evaporated under reduced pressure for 20 minutes. Then another portion of solvent (10ml) was added and the solution was evaporated again for 20 minutes. The reaction mixture was left at 20-40°C for 2-24 h. The dihydroperoxide was purified by column chromatography.

§Large-scale experiment: On a 10-mmol scale, 2-times 20 mL of MeCN was used. After the end of reaction mixture was diluted with dichloromethane, a catalytic amount of MnO_2 was added and stirred to decompose excess of H_2O_2. Organic phase was dried with Na_2SO_4, solids filtered off and pure **2a** obtained after evaporation of the solvent.

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