Letter

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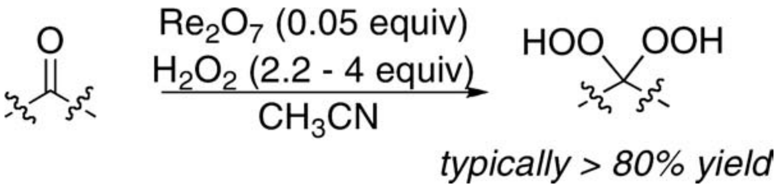

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Mild and Efficient Re(VII)-Catalyzed Synthesis of 1,1-Dihydroperoxides

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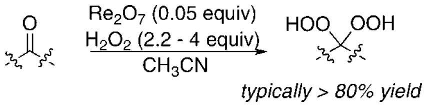
ABSTRACT



Re_2O_7 in CH_3CN is a remarkably efficient and mild catalyst for the peroxyacetalization of ketones, aldehydes, or acetals by H_2O_2 to generate 1,1-dihydroperoxides. $Me_3SiOReO_3$ and methyl rhenium trioxide (MTO) are also effective catalysts under these reaction conditions.

1,1- or *gem*-dihydroperoxides are stable derivatives of ketones and aldehydes[1] and important intermediates in the synthesis of a number of classes of peroxides, including tetraoxanes,[2] silatetraoxanes,[3] spirobisperoxyketals,[4] bisperoxyketals,[5] and 1,2,4,5-tetraoxacycloalkanes.[6] Dihydroperoxides have also been employed as initiators for radical polymerization reactions,[7] as reagents for nucleophilic epoxidations and oxidations,[8,9] and as precursors for synthesis of dicarboxylic acid diesters.[10] We now report that Re_2O_7-catalyzed peroxyacetalization of ketones and aldehydes furnishes 1,1-dihydroperoxides in high yields and with a broader substrate scope than any existing catalyst system.[11]

Of the methods described for the synthesis of 1,1-dihydroperoxides, most have significant limitations.[1] The direct reaction of ketones with commercial grades of aq. H_2O_2, in either the presence or the absence of formic acid,[6,12] proceeds in modest yield.[1] The reaction of H_2O_2 with enol ethers, ketals, aldehydes, or ketones in the presence of strong Brönsted or Lewis acids is widely applied[13−16] but can face problems with heterolytic rearrangements.[17,18] Iodine-promoted peroxyacetalization proceeds under mild conditions and achieves good yields[19] but requires long reaction times and is likely limited to saturated substrates. The use of ceric ammonium nitrate as a catalyst requires a large excess of H_2O_2 and may be limited by the sensitivity of the substrate

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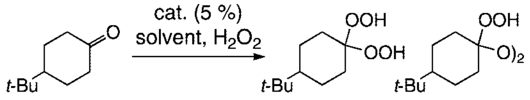
or product toward oxidation.[20] Ozonolysis of alkenes in the presence of H_2O_2 allows preparation of 1,1-dihydroperoxides under neutral conditions but requires the use of organic solutions of H_2O_2 and is limited to ozone-compatible substrates.[4,21]

Methyl rhenium trioxide (MTO) catalyzed peroxyacetalization of cycloalkanones and aldehydes has been applied in tandem with ketalization of the intermediate dihydroperoxides as an approach to unsymmetric 1,2,4,5-tetraoxanes.[22−24] However, the method requires fluorinated alcohol solvents and has not been applied to aliphatic substrates. We became interested in Re_2O_7, which has been applied to the isomerization/deprotection of allyl silyl ethers[25] and, in conjunction with TFAA, the ring opening of THF.[26] Silylated perrhenates are known to catalyze the isomerization of unsaturated alcohols.[27]

A preliminary investigation of the peroxyacetalization of 4-*t*-butylcyclohexanone (**1a**) with a modest excess of aq. H_2O_2 in CH_3CN revealed the formation of useful yields of the dihydroperoxide (**2a**) in the presence of MTO, Re_2O_7, or $Me_3SiOReO_3$ (Table 1); in each case, the desired product was accompanied by small amounts of the bishydroperoxy peroxide (**3a**). Although higher yields were obtained with Re_2O_7 or $Me_3SiOReO_3$, the catalytic activity of MTO is noteworthy, given the lack of a fluorinated alcohol additive.[21−23] Solvent polarity appears important, as the peroxyacetalization proceeded more rapidly and in higher yield in CH_3CN compared with CH_2Cl_2. Conducting the Re_2O_7-promoted reaction at 0 °C slowed the reaction but resulted in a higher yield and the absence of byproducts. Considerations of cost and convenience led us to focus on Re_2O_7.[28,29]

Table 1. Comparison of Re(VII) Catalysts



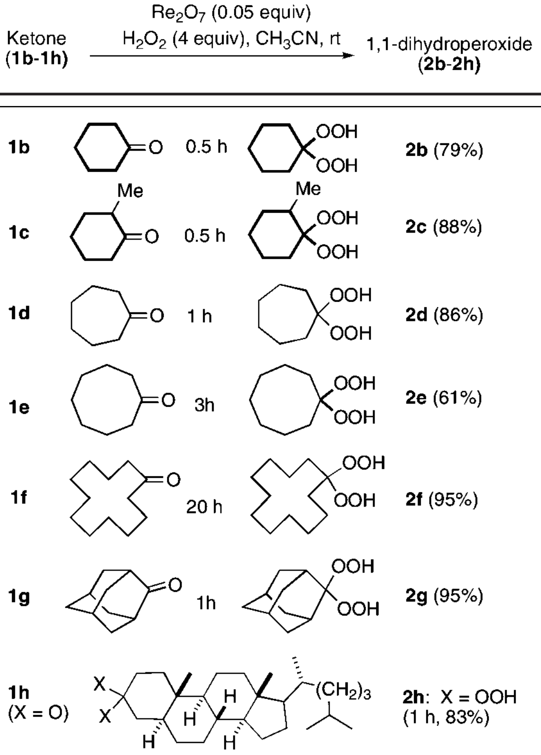
1a **2a** **3a**

catalyst	solvent	H_2O_2 (equiv)	temp	time (h)	**2a** (%)[a]	**3a** (%)[a]
MTO	CH_3CN	4	rt	0.5	73	3
Re_2O_7	CH_3CN	4	rt	0.5	86	5
	CH_3CN	2.2	0 °C	1	95	–
	CH_2Cl_2	2.2	rt	0.5	41	30
$Me_3SiOReO_3$	CH_3CN	2.2	rt	0.5	81	5

[a] Isolated yields.

Application to the synthesis of cyclic-1,1-dihydroperoxides is summarized in Table 2. The six- and seven-membered ring ketones, including adamantanone, provided excellent yields of the dihydroperoxides in an hour or less. Cyclooctanone reacted slowly and gave the lowest yield within this group. The reaction of cyclododecanone, while even slower, furnished the dihydroperoxide in excellent yield. Traces of bishydroperoxyperoxide dimers were often observed (TLC) in the crude reaction mixtures but were lost upon chromatography. No products of ring expansion were observed except for **1d**, where the product (**2d**) was accompanied by approximately 5% of octalactone.[30]

Table 2. Synthesis of Cycloalkyl-1,1-dihydroperoxides



With the exception of iodine-catalyzed peroxyacetalizations,[19] preparation of acyclic 1,1-dihydroperoxides has been problematic, particularly for aldehydes or aryl ketones. This limitation presumably reflects the tendency of the intermediate perhydrate or the dihydroperoxides to undergo heterolytic

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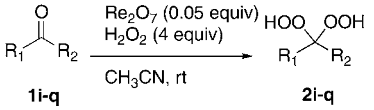
fragmentations.[17,18] We were therefore pleased to observe that the peroxyacetalizations proceed in good to excellent yield for aliphatic ketones, aromatic aldehydes, and aromatic ketones (Table 3). Aromatic aldehydes and ketones generally required longer reaction times; at the extreme, only traces of product were observed from reaction of 4-nitrobenzaldehyde. The lower yields obtained for substrates **1m** and **1q** appear due to oligomerization of the electron-rich products (**2m**, **2q**) under the reaction conditions.

Table 3. Synthesis of Acyclic 1,1-Dihydroperoxides



substrate	R_1	R_2	time(h)	product	yield
1i	pentyl	Me	0.5	**2i**	94%
1j	$Ph(CH_2)_2$	Me	1	**2j**	89%
1k	Bu	Bu	1	**2k**	71%
1l	Ph	H	6	**2l**	96%
1m	4-MeOPh	H	2	**2m**	67%
1n	2-MeOPh	H	5	**2n**	94%
1o	3-MeOPh	H	5	**2o**	92%
1p	4-ClPh	H	5	**2p**	96%
	$4-NO_2Ph$	H	24	–	–[a]
1q	Ph	Me	24	**2q**	69%

[a] Traces of product decomposed during purification.

Finally, Re_2O_7 was also found to catalyze the peroxyacetalization of benzaldehyde dimethyl acetal (Figure 1), although in lower yield than had been obtained from the corresponding aldehyde (see Table 3).

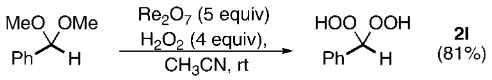


Figure 1. Re(VII)-catalyzed peroxyacetalization of an acetal.

Reactions such as the acetal exchange can reasonably be attributed to Brønsted acid catalysis.[31] However, the higher yields and improved scope relative to more traditional catalysts points to a different mode of substrate or reagent activation. This is supported by the activity of MTO, a catalyst unlikely to generate a potent Brönsted acid under the reaction conditions. The demonstrated activation of alcohols by silyl perrhenates[27] suggests that our results may be due to Re(VII) activation of the intermediate perhydrate.

In conclusion, Re_2O_7-catalyzed peroxyacetalization offers a mild, efficient, and broadly applicable method for synthesis of 1,1-dihydroperoxides which employs an inexpensive organic solvent and requires only a slight excess of H_2O_2.[32] Application of this methodology for the chemoselective synthesis of 1,2,4,5-tetraoxanes is in progress.

Acknowledgment. This work was funded by NSF CHE 0749916. NMR spectra were acquired, in part, on spectrometers purchased with NSF support (MRI 0079750 and CHE 0091975). A portion of this research was conducted in facilities remodeled with support from the NIH (RR016544-01). We thank Prof. Jonathan Vennerstrom (Univ. of Nebraska-Medical Center) for useful discussions.

Supporting Information Available: Details regarding preparation and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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