ORGANIC LETTERS

2009
Vol. 11, No. 1
213−216

Broadly Applicable Synthesis of 1,2,4,5-Tetraoxanes

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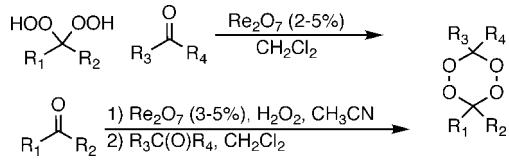
Received October 16, 2008

ABSTRACT



Re_2O_7 is a mild and efficient catalyst for the high-yielding condensation of 1,1-dihydroperoxides with ketones or aldehydes to form 1,2,4,5-tetraoxanes, including targets not easily prepared via existing methodology. When applied in tandem with a recently reported Re(VII)-catalyzed synthesis of 1,1-dihydroperoxides, the reaction provides a high-yielding one-pot conversion of ketones or aldehydes to tetraoxanes.

The identification of the natural product artemisinin from a traditional Chinese herbal remedy opened a new frontier in antimalarial chemotherapy based upon the use of therapeutics containing a peroxide pharmacophore (Figure 1).[1−4] Al-

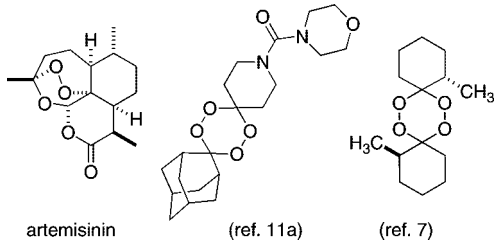


Figure 1. Artemisinin and antimalarial 1,2,4,5-tetraoxanes.

though artemisinin and several semisynthetic analogs are now used clinically against drug-resistant strains of *Plasmodium falciparum*, there are several good reasons to pursue development of alternative peroxide-based antimalarials. First, the artemisinins have limitations in terms of availability, cost, and the requirement for a weeklong treatment regimen. Moreover, an expansion of structural diversity could help to extend the therapeutic utility of peroxide antimalarials in the event of the emergence of artemisinin-resistant strains.[5] The search for new leads has brought renewed attention to 1,2,4,5-tetraoxanes,[6] a class of peroxides recently found to combine antimalarial activity with chemical stability (Figure 1).[4,7−9] However, the synthesis of functionalized tetraoxanes remains quite problematic.

Symmetric 1,2,4,5-tetraoxanes have been prepared through reaction of ketones with acidic hydrogen peroxide,[10] or through dimerization of the carbonyl oxides derived from

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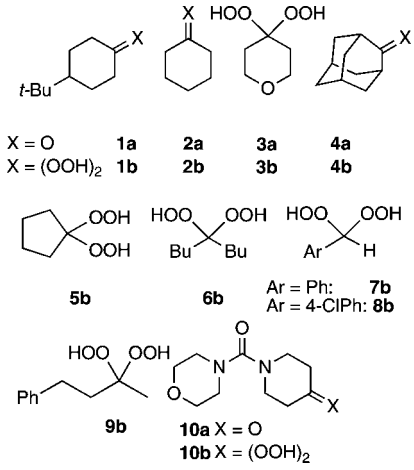
10.1021/ol8023874 CCC: $40.75
Published on Web 12/09/2008

tetrasubstituted alkenes, enol ethers, or oximes.[11] A handful of 1,2,4,5-tetraoxanes have been prepared through decomposition of ozonides in the presence of $SbCl_5$ or chlorosulfonic acid.[12] However, the majority of existing syntheses are based upon Brönsted or Lewis acid-catalyzed condensation of a 1,1-dihydroperoxide with an aldehyde, ketone, or acetal.[4,8,13] The strongly acidic conditions of these condensations are incompatible with many functional groups and can result in decomposition of the tetraoxanes or their dihydroperoxide precursors (vida infra). In the course of recent investigations of Re_2O_7-promoted bisperoxyacetalization of ketones and aldehydes,[14] we observed slow oligomerization of the product dihydroperoxides if the reaction solutions were allowed to stand for prolonged periods. We became curious as to whether Re(VII) species could also promote condensations of dihydroperoxides with ketones and aldehydes. We now report a new method for tetraoxane synthesis based upon Re(VII)-promoted condensation of 1,1-dihydroperoxides and carbonyls. The transformation, which can be applied to isolated dihydroperoxides or in tandem with Re(VII)-mediated peroxyacetalization of carbonyls, provides superior yields for a broader scope of substrates compared with any existing methodology.

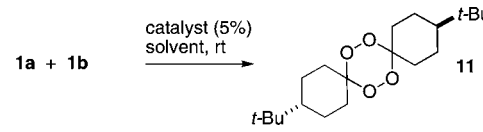
The 1,1-dihydroperoxides were available in high yield through Re_2O_7-catalyzed peroxyacetalization of ketones or aldehydes. (Scheme 1).[14]

Scheme 1. Ketones and Dihydroperoxides in This Study



Our initial investigations, illustrated in Table 1, compared three commercially available Re(VII) catalysts for the ability to catalyze condensation of 4-*t*-butyl-1,1-dihydroperoxycyclohexane (**1b**) with 4-*t*-butylcyclohexanone (**1a**) to form a symmetric 1,2,4,5-tetraoxane (**11**). In all cases, tetraoxane **11** was generated as a single diastereomer.

Table 1. Comparison of Re(VII) Catalysts for Condensation of Dihydroperoxide and Ketone

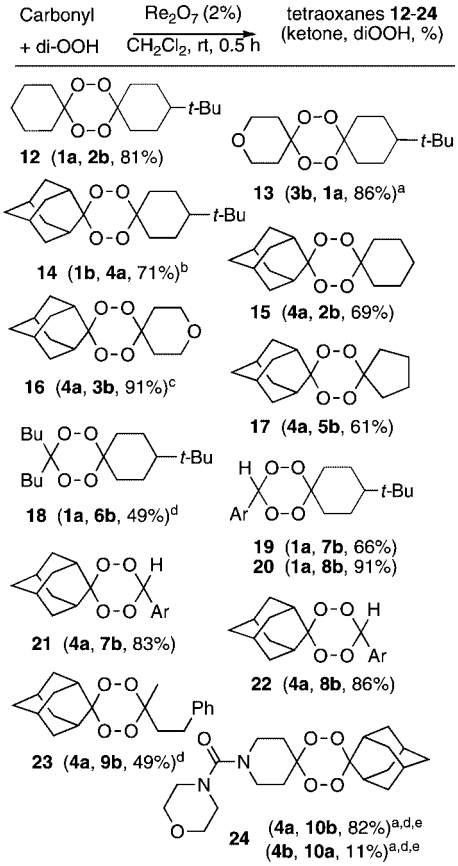


catalyst	solvent	time (h)	**11** (%)[a]
MTO	CH_2Cl_2	0.5	23
Re_2O_7	CH_3CN	0.5	66
Re_2O_7	CH_2Cl_2	0.5	81
$Me_3SiOReO_3$	CH_2Cl_2	0.5−1	78

[a] Isolated yield.

Although the highest yields were obtained with Re_2O_7 or $Me_3SiOReO_3$, the catalytic activity of MTO is noteworthy given that this reagent has previously been employed only for synthesis of 1,1-dihydroperoxides; subsequent condensa-

Scheme 2. Condensation of Ketones with 1,1-Dihydroperoxides



[a] CF_3CH_2OH as solvent. [b] 64% on 1 g scale. [c] CH_3CN/CH_2Cl_2 1:5 as solvent. [d] Reaction time 1 h. [e] Five mol % Re_2O_7.

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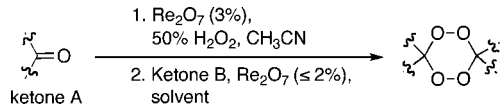
Table 2. One-Pot Synthesis of Tetraoxanes from Ketones



conditions, step 1	conditions, step 2	tetraoxane (yield)
1a, H_2O_2 (2 equiv), 0.5 h, 0 °C	**4a** (2 equiv), CH_2Cl_2, 1 h, rt	**14** (67%)[a]
1a, H_2O_2 (4 equiv), 0.5 h, rt	**4a** (4 equiv), CF_3CH_2OH, Re_2O_7 (2%), 0.5 h, rt	**14** (51%)
3a, H_2O_2 (4 equiv), 0.5 h, rt	**4a** (4 equiv), CF_3CH_2OH, Re_2O_7 (2%), 0.5 h, rt	**16** (69%)[b]
10a, H_2O_2 (4 equiv), 6 h, rt	**4a** (4 equiv), CF_3CH_2OH, Re_2O_7 (2%), 2 h, rt	**24** (49%)

[a] Includes 3−5% of homodimeric tetraoxane **11**. [b] 59% yield on 1 g scale.

tions with ketones employed added Brønsted acid.[13a,15] The Re_2O_7- and $Me_3SiOReO_3$-promoted condensations proceeded rapidly in CH_2Cl_2, allowing complete conversion to tetraoxane in 30 min or less. All further experiments focused on Re_2O_7.

Re_2O_7 was investigated as a catalyst for the condensation of a series of 1,1-dihydroperoxides with ketones to form nonsymmetric 1,2,4,5-tetraoxanes **12**−**24** (Scheme 2). Reactions were conducted in the presence of 2% catalyst and were typically complete in 30 min. The reactions initially employed equimolar amounts of ketone and dihydroperoxide. Although yields were generally good, we occasionally observed the formation of symmetric 1,2,4,5-tetraoxane byproducts. For compounds in which the two skeletal components differed significantly in composition or polarity, the desired product and the homodimeric byproduct could be easily distinguished by TLC. However, in other cases, the homo- and heterodimers were only distinguishable by ESI-HRMS. In no case could we detect the presence of any hexaoxane trimers.[16a,b] The formation of symmetric byproduct could be minimized by using a 1.5:1 stoichometry of ketone to dihydroperoxide and by filtering the reaction through a plug of silica as soon as the dihydroperoxide could no longer be observed by TLC. CH_3CN/CH_2Cl_2 or CF_3CH_2OH could be used as solvents in cases where CH_2Cl_2 solubility was an issue. The reaction is scalable, as evidenced by a gram-scale preparation of **14**. For tetraoxane **24**, we explicitly investigated synthesis from both possible ketone/dihydroperoxide combinations. The large difference in product yield appears to reflect the limited stabilty of **4b** under the reaction conditions. As has been observed by others,[16a,b] some tetraoxanes exhibit complex conformational behavior. For example, several of the products which were clearly homogeneous (HPLC, HRMS) exhibited a larger than expected number of ^{13}C NMR signals, many of which began to coalesce upon reacquisition of spectra at 60 °C.

Re_2O_7 and a Brønsted acid (H_2SO_4) were explicitly compared for the ability to catalyze the synthesis of tetraoxane **14** (eq 1). Whereas the Re_2O_7-promoted process proceeded in 71% yield, the corresponding condensation in the presence of H_2SO_4 proceeded in 29% yield. Control reactions suggested that the low yield in the latter case results from the instability of both the dihydroperoxide and the tetraoxane under the strongly acidic reaction conditions. In contrast, tetraoxanes **13**−**24** were unchanged by exposure to the Re_2O_7 catalyst for at least two hours, a period 4-fold longer than our typical reaction times.

$$\mathbf{1b} + \mathbf{4a} \rightarrow \mathbf{14}$$
$$\begin{array}{ll} Re_2O_7(0.02\ \text{equiv}),\ CH_2Cl_2,\ \text{rt},\ 0.5\ \text{h} & 71\,\% \\ H_2SO_4(2.5\ \text{equiv}),\ CH_3CN,\ 0\ ^\circ\text{C},\ 2\ \text{h (ref 9)} & 29\% \end{array} \quad (1)$$

Given that the Re_2O_7-catalyzed bisperoxyacetalization of ketones and aldehydes[14] is conducted in CH_3CN whereas the subsequent condensation of dihydroperoxides and carbonyls proceeds much more rapidly in CH_2Cl_2, we were curious about the potential of a one-pot, two-solvent approach for the synthesis of unsymmetric 1,2,4,5-tetraoxanes. The results are illustrated in Table 2. Addition of 2–4 equiv of 50% aq. H_2O_2 to a solution of ketone (1.0 equiv) and Re_2O_7 (0.05 equiv) in CH_3CN led to rapid consumption of the ketone. Once the ketone could no longer be detected (typically less than 0.5 h, TLC), the reaction was partially concentrated at reduced pressure, and the second ketone added as a solution in CH_2Cl_2. A rapid and slightly exothermic reaction ensued to generate the desired 1,2,4,5-tetraoxanes. The use of CH_2Cl_2 as the solvent for the second step sometimes resulted in formation of small amounts (3−5%) of the homodimeric tetraoxanes derived from the initial ketone. Although these byproducts were in general easily removed by chromatography, we found their formation could be almost completely suppressed by conducting the condensation step in CF_3CH_2OH. As can be seen in Table 2, the yields for the one-pot process are quite good, including a 59% yield for a gram-scale preparation of tetraoxane **16**, and a 49% yield for tetraoxane **24**, an antimalarial candidate previously available in 6% yield by a one-pot route involving MTO-promoted peroxyacetalization followed by Brønsted acid-promoted condensation of the dihydroperoxide with a ketone.[13a]

The mechanism of tetraoxane formation almost certainly begins with reversible addition of the dihydroperoxide to the ketone or aldehyde. The resulting hydroperoxy/hydroxy

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peroxide can undergo the desired cyclocondensation to a tetraoxane, or, alternatively, oligomerization to a hexaoxane. In contrast to the strongly acidic conditions employed in most existing approaches, the Re_2O_7-promoted condensations proceed rapidly under conditions compatible with both dihydroperoxides and tetraoxanes. Re(VII)-oxo catalysts have been previously applied for the bisperoxyacetalization of ketones,[14] the isomerization of unsaturated alcohols,[17] the isomerization/deprotection of allyl silyl ethers,[18] and the ring opening of tetrahydrofuran.[19] The high activity of the Re(VII) species, and in particular the ability to achieve cyclocondensation of the hydroxy/hydroperoxy peroxides under mild conditions, may reflect the ability to activate the perhydrate derived from addition of H_2O_2 to the ketone. This hypothesis is supported by a recent report describing the ability of Re_2O_7 or triphenylsilylperrehenate to catalyze Prins cyclizations of aldehydes and alkenols.[20]

In conclusion, Re_2O_7 in CH_2Cl_2 offers a mild and highly efficient catalyst for the condensation of carbonyl groups with 1,1-dihydroperoxides to form 1,2,4,5-tetraoxanes. In tandem with the Re_2O_7-promoted bisperoxyacetalization of aldehydes and ketones, the new methodology offers a high-yielding and one-pot method for synthesis of tetraoxanes.

Acknowledgment. This work was funded by NSF CHE 0749916 in facilities remodeled with support from NIH (RR016544-01). NMR spectra were acquired, in part, on spectrometers purchased with NSF support (MRI 0079750 and CHE 0091975). We thank Profs. Jonathan Vennerstrom and Yuxiang Dong (University of Nebraska Medical Center) and Prof. Scott Rychnovsky (University of California at Irvine) 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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