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Synthesis of 1,2-Dioxanes, 1,2,4-Trioxanes, and 1,2,4-Trioxepanes via Cyclizations of Unsaturated Hydroperoxyacetals

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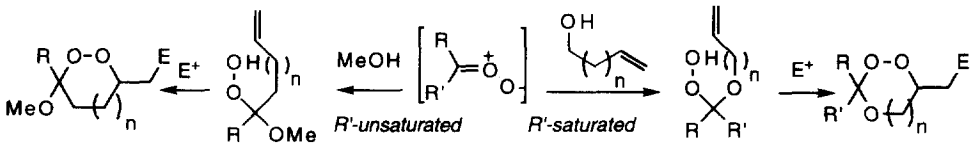
Abstract: Unsaturated hydroperoxyacetals and -ketals undergo electrophilic cyclization to afford dioxanes, trioxanes or trioxepanes. Stereoselectivity is low for trioxepanes, moderate for dioxanes, and high for trioxanes. The hydroperoxide starting materials are readily prepared through selective ozonolysis of an enol ether in the presence of an internal or external alkene.

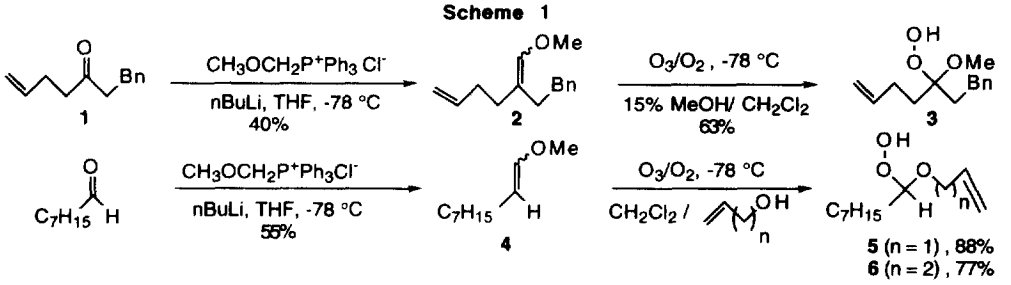
The discovery of pharmacologically active six- and seven-membered ring peroxides has placed a renewed emphasis on stereoselective methods for hydroperoxide cyclization.[1] The electrophilic or radical cyclization of unsaturated hydroperoxides has been investigated by a number of groups as a strategy for producing 1,2-dioxolanes, 1,2-dioxanes, and 1,2,4-trioxanes.[2,3] While the cyclizations generally proceeded in good yield, the overall efficiency of this strategy is often limited by low yields in the synthesis of the hydroperoxide precursor. We now report an improved route to dioxanes, trioxanes, and trioxepanes based upon cyclization of unsaturated hydroperoxyacetals or -ketals derived through trapping of ozonolysis-derived carbonyl oxides (Fig. 1).

Figure 1



An initial substrate was prepared through chemoselective ozonolysis of an enol ether in the presence of a remote alkene. Methoxymethylenation of 1-phenyl-6-hepten-3-one **1**, available through benzylation of the hydrazone derived from 5-hexen-2-one, produced enol ether **2**. Ozonolysis in the presence of methanol afforded hydroperoxyketal **3**. Stoichometric ozonolysis frequently led to significant amounts of over oxidized material. However, intentional substoichometric ozonolysis provided good yields of **3** accompanied by small amounts of enol ether starting material.

Scheme 1



A second series of substrates was produced through ozonolysis of an enol ether in the presence of an unsaturated alcohol.[4] Enol ether **4**, derived through methoxymethylenation of octanal, underwent ozonolysis in the presence of allyl alcohol or 3-buten-1-ol, as co-solvents, to afford hydroperoxyacetals **5** and **6**, respectively.

Cyclizations of simple 4-alkenyl hydroperoxides are known to produce 1,2-dioxanes through chair-like transition states.[5] At first glance, hydroperoxyketal **3** might appear to suffer from conflicting steric demands; the presence of a *gem*-disubstituted center in a forming dioxane ring results in reduced stereoselection (Scheme 2).[6] However, stereoelectronic effects should favor a chair-like transition state in which the alkoxide group preferentially assumes an axial position. Anomeric interactions have been documented qualitatively for alkoxydioxanes;[7] related 2-alkoxytetrahydropyrans favor an axial alkoxide by approximately 0.8 kcal/mole.[8] Although a variety of reagents have been employed for electrophilic cyclization of unsaturated hydroperoxides, maximum stereoelectronic influence by the acetal center would be favored by reactions featuring a late, dioxane-like, transition state. Iodine was initially chosen based upon analogy with iodolactonizations, in which the product stereochemistry is influenced by a nucleophile-dependent transition state.[9] Peroxyiodination in the presence of pyridine provided **7a** and **7b** in respectable yield but with a complete lack of diastereoselection. Cyclization in the presence of amine bases led to poorer yields, in part due to decomposition of the base-labile peroxyacetals.[10] Surprisingly, addition of potassium *tert* -butoxide, either in the presence or absence of a crown ether, resulted in modest selectivity for formation of the diastereomer (**7b**) with an axial iodomethyl side chain. The stereoelectronic influence of the peroxyacetal center, although difficult to assess in the transition state, is clearly present in the alkoxydioxane products; equilibration of the two diastereomers in acidic methanol afforded a 3:1 mixture enriched in diastereomer **7a**. All products were fully characterized; stereochemical assignments are based upon the magnitude of the H_5-H_6 coupling constants.

Scheme 2

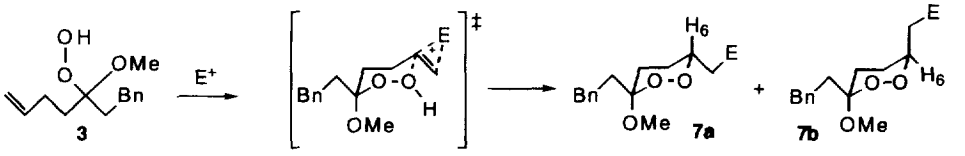


Table 1 : Dioxane Synthesis

Reagent	E	Temp.	Solvent	Yield	7a : 7b
pyridine / I_2	I	0 °C	CH_2Cl_2	50%	1 : 1*
tBuOK / I_2	I	rt	THF	48%	1 : 1.7 *
tBuOK / I_2 /18-C-6	I	rt	benzene	34%	1 : 2.5 *
1. $Hg(OAc)_2$ 2. KBr	HgBr	rt	CH_2Cl_2	55%	3 : 1 *
1. $Hg(OAc)_2$ 2. KBr	HgBr	-78 °C	CH_2Cl_2	46%	1.5 : 1 **

* Diastereoselectivity determined by ^1H NMR **Diastereoselectivity determined by mass balance

We next turned to peroxymercuration, a standard method for peroxide cyclization which had nonetheless received lower initial priority based on the assumption that formation of the mercurinium ion would occur without influence from the hydroperoxyacetal. We were therefore surprised to find that reaction with mercuric acetate selectively furnished **7a** in good yield. The reversal of diastereoselectivity between kinetic peroxymercuration and base-mediated peroxyiodination is not yet understood but appears to provide a route for selective synthesis of either diastereomer.

Next an attempt was made to cyclize unsaturated hydroperoxyacetals to form 1,2,4-trioxanes, the core element of the potent anti-malarial artemisinin (Scheme 3).[11] Hydroperoxyacetal **5** did not undergo cyclization in the presence of iodine and pyridine, conditions which had been successful for hydroperoxyketal **3**. Increasing the electrophilicity of iodine with silver salts or through replacement by iodine monochloride also failed to provide trioxanes. Cyclization was successful, however, for the corresponding peroxyanions. The lithium salt, produced through deprotonation of the hydroperoxyacetal with *n*-BuLi, underwent reaction to produce a modest yield of trioxane with high selectivity for the equatorial isomer (**8a**). Substitution of a potassium base (KH or KO*t*Bu) resulted in a much faster reaction with similar overall yield and moderate selectivity for production of **8a**. Cesium-promoted cyclization proceeded rapidly with high diastereoselection but reduced yield. The sensitivity of both the starting materials and products towards base-mediated peroxide fragmentation cautions against too literal a comparison between the examples involving lithium, potassium, and cesium bases.[12] Although never completely suppressed, fragmentation could be minimized through the use of nonpolar solvents.

Scheme 3

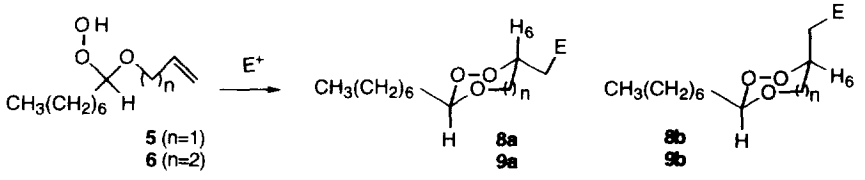


Table 2 : Trioxane Synthesis

Reagent	E	Temp.	Solvent	Yield	8a : 8b
1. nBuLi 2. I_2	I	- 78 °C	THF	20%	10 : 1 *
1. KH 2. I_2	I	0 °C - rt	THF	24%	7 : 1 **
tBuOK / I_2	I	0 °C	CH_2Cl_2	19%	4 : 1 **
tBuOK / I_2, 18-C-6	I	rt	C_6H_6	22%	6 : 1 *
Cs_2CO_3 / I_2	I	rt	THF	12%	10 : 1 **
1. $Hg(OAc)_2$ cat. $HClO_4$ 2. KBr	HgBr	rt	CH_2Cl_2	85%	1.5 : 1 *
1. $Hg(OAc)_2$ 2.KBr	HgBr	rt	CH_2Cl_2	64%	10 : 1 *

* diastereoselectivity determined by ^1H NMR. ** diastereoselectivity determined by mass balance.

For similar reasons as described earlier, we had initially reasoned that peroxymercuration would result in poor diastereoselection. To our surprise, peroxymercuration with mercuric acetate proceeded in high yields with diastereoselection rivaling the best results with iodine. The high diastereoselectivity of trioxane formation through either peroxyiodination or peroxymercuration clearly resulted from transition state bias; peroxymercuration under thermodynamic conditions (catalytic perchloric acid) proceeded in higher yield but with greatly reduced diastereoselectivity.[13] The crude organomercurials were characterized after exchange to the mercuriobromides, which could be oxidized to the alkyl iodide with no change in diastereoselection. The superior diastereoselectivity seen in the trioxane series relative to the dioxane series is yet to be understood. It is interesting to compare our strategy with a novel approach recently reported by Bloodworth and co-workers in which cyclization of peroxyhemiacetals derived through interaction of aldehydes with allyl hydroperoxides is used to produce 1,2,4-trioxanes.[13]

Hydroperoxyacetal cyclizations could also be extended to the synthesis of trioxepanes (Scheme 3 and Table 3). Peroxymercuration of acetal **6** was successful, albeit in low yield, to afford a nearly

random mixture of trioxepanes **9a** and **9b**. The trioxepanes were less stable than the corresponding trioxanes. No trioxepanes were isolated from peroxyiodination, even though the hydroperoxyacetal was consumed under the reaction conditions.

Table 3: Trioxepane Synthesis

Reagent	E	Temp.	Solvent	Yield	9a : 9b
tBuOK / I_2 10 mol % 18-C-6	I	rt	C_6H_6	decomposed	
1. $Hg(OAc)_2$ 2. HgBr	HgBr	0 °C	CH_2Cl_2	69% conv. 26% yield	1.1 : 1 *

* diastereoselectivity determined by ^1H NMR.

In conclusion, cyclization of ozonolysis-derived unsaturated hydroperoxyacetals provides a new strategy for rapid assembly of cyclic peroxides. The use of a chiral carbonyl oxide or a chiral alcohol may offer a practical method for asymmetric synthesis of cyclic peroxides. Further studies are in progress and will be reported in due course.

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