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ALKOXY RADICALS IN ORGANIC SYNTHESIS. A NOVEL APPROACH TO SPIROKETALS

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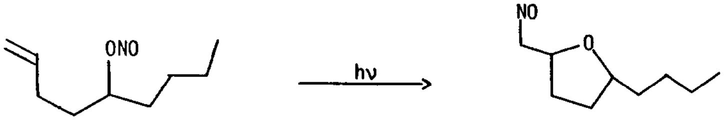
Abstract: Photolysis of an unsaturated alcohol in the presence of HgO and iodine generates an alkoxy radical which can cyclize to form a five-membered ring ether. If a hemiketal is employed, a spiroketal can be formed in good yield.

In recent years the use of radical chemistry in organic synthesis has seen explosive growth. Radical cyclizations have been employed in the synthesis of alkaloids, terpenes and other natural products. Most of the research has been collated in reviews[1] and a timely monograph.[2] In contrast to the volume of work on carbon centered radicals, the use of alkoxy radicals in synthesis has been limited.[3] A most notable example is remote functionalization by photolysis of nitrite esters which has been elegantly developed by Barton and coworkers.[4] Feldman has recently reported a promising application of hydroperoxy radicals in synthesis.[5]

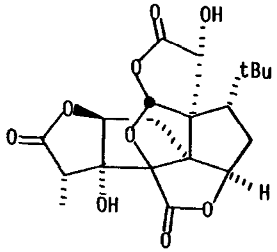
The infrequent use of alkoxy radicals for C-O bond formation is in part due to the competitive hydrogen atom abstraction reaction which often ensues. Surzur has shown that the intermolecular reaction of an alkoxy radical with an alkene affords largely products derived from hydrogen atom abstraction.[6] However, when the alkoxy radical is generated in a molecule bearing a proximate alkene, the addition reaction to form a cyclic ether can become the sole pathway. An example of this behavior has been discovered by Rieke and is depicted below.[7]

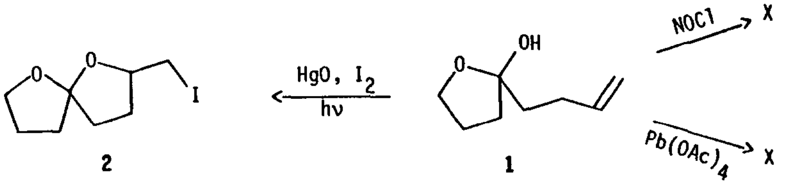


Surprisingly, only a few examples of this potentially useful reaction have been reported.[3a-g] In most of the cases the alkoxy radical was generated by photolysis of a nitrite ester.

The formation of ethers by a radical reaction has some advantages over its ionic counterparts. Ether formation from alcohols and alkenes has been accomplished by oxymercuration,[8] iodoetherification[9] and selenenoetherification reactions.[10,11] With many intramolecular examples, the ring size is dictated by the substitution pattern on the alkene. In some cases the reaction fails or proceeds in poor yields when electron withdrawing substituents are conjugated with the alkene. In contrast, the intramolecular addition of radicals to alkenes affords products derived from a 5-exo-trig type attack. The electronic effect of a substituent is not as important as its steric effect.

In connection with a synthetic approach to the ginkgolides,^{12} the synthesis of certain spiroketals became necessary. Because we envisioned C-O bond formation to an electron-deficient alkene, we initially examined a radical addition pathway in the model system shown below. This system was readily prepared by the addition of butyrolactone to a solution of 3-butenylmagnesium bromide in tetrahydrofuran at 0°C followed by workup with ammonium chloride. Despite several attempts, the desired nitrile ester could not be generated. Since ethers have been formed by the treatment of olefinic alcohols with lead tetraacetate under conditions which favor the production of radicals,^{13} we next subjected the hemiacetal 1 to lead tetraacetate and pyridine in boiling benzene. Unfortunately, these conditions also led to the formation of complex mixtures of products. After other unsuccessful ventures, the photochemically initiated reaction of 1 with mercuric oxide and iodine afforded a 68% isolated yield of spiroketal 2.^{14} Unexpectedly, the proton and carbon NMR spectra both indicated that only one stereoisomer had been formed.





Since these reaction conditions had never been used to effect alkoxy radical additions to alkenes, several representative olefinic alcohols were then examined to assess the scope of this procedure. The results are depicted in Table 1. From the results in Table 1, the HgO/I_2 conditions appear to be the most general conditions yet found. However, this procedure still has its limitations, as evidenced by entries 4 and 5. It is possible that 3-hydroxyethyl cyclopentene cyclized in low yield because of a competing intramolecular hydrogen atom abstraction reaction. The transition state for the alkoxy radical addition reflects the strain inherent in a bicyclo[3.3.0]octane, thereby allowing the less strained hydrogen atom abstraction reaction to intervene. Fragmentation of the alkoxy radical to formaldehyde and an alkyl radical could also occur. One attempt to form a six-membered ring (entry 5) produced a modest yield of the desired product.

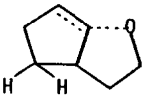
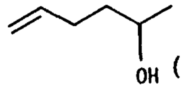
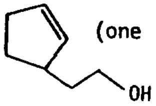
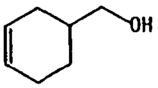
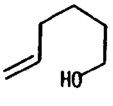
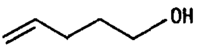
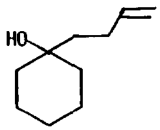
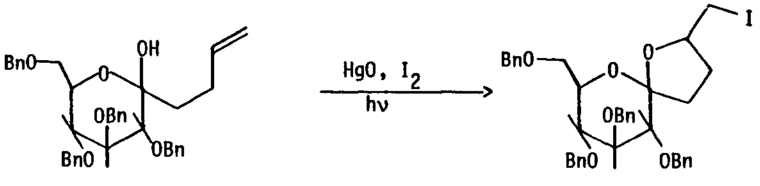


Table 1. Radical cyclizations

Entry		% yield[a]	Entry		% yield[a]
1	 (1:1 mix of isomers)	60	4	 (one isomer)	17
2		55[17]	5		39
3		50	6		34

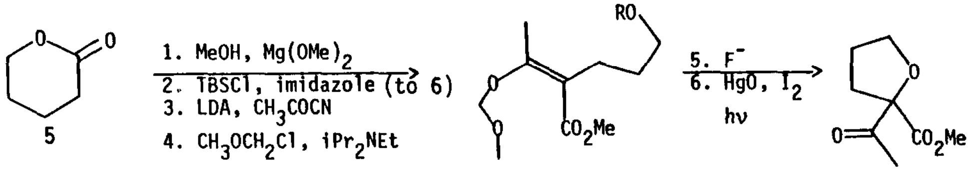
[a] Yields represent chromatographed products whose NMR, C-13 NMR, IR and mass spectra/ analysis are consistent with assigned structures.

In view of the encouraging results from Table 1, we then synthesized hemiketal 3 from gluconolactone.[15] Under our best reaction conditions, the yield of 4 was 53%. Typical experimental conditions involve the photolysis (medium pressure Hanovia lamp) of a stirred, cooled (0°C) suspension of mercuric oxide (3 eq.) in benzene containing the alcohol (1 eq.) and iodine (3 eq.) for three hours. The crude product is filtered, washed with 10% sodium bisulfite solution, concentrated and chromatographed on silica gel. Cooling the reaction mixture is important, since the yields of purified product are about 10-15% lower when the photolysis is conducted at ambient temperature. The type of HgO had no effect on the yield. Traces of products were formed in the absence of light.



3 4

While the intermediacy of alkoxy radicals is likely, particularly in light of Barton's results,[14] one cannot rule out an extremely rapid ionic addition of a hypoiodite to the alkene. The intramolecular addition shown below would offer some insight into this question and in addition provide a close precedent for the ginkgolide system. Alcohol 7 was produced from valerolactone by opening of 5 with methanol and a catalytic amount of magnesium methoxide. The resulting primary alcohol was silylated with t-butyldimethylsilyl (TBS) chloride and imidazole. Ester 6 was then deprotonated (LDA, THF, -78°C) and reacted with acetyl cyanide[16] to produce the ketoester in 75% yield. The ketoester was deprotonated (NaH, THF, 0°C) and then O-alkylated to form the MOM ether with chloromethylmethyl ether. The silyl



5 7 R = H 8

ether was deprotected to afford 7. When 7 was treated with our standard conditions, a 45% yield of 8 was obtained. The MOM ether had been selected because it should promote the fragmentation which afforded the ketone. The cyclization to produce the five-membered ring ether is consistent with a radical addition. Ionic addition of a hypoiodite would have produced a six-membered ring.

The chemistry described herein provides a mild and reliable method for the generation of alkoxy radicals and also extends their synthetic utility. The conversion of 7 to ether 8 supports our projected route to the ginkgolides. The radical-based approach to spiroketals is distinctly different from previous methods and offers a useful alternative.

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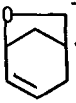
17. Dehydrohalogenation with DBN afforded . This product was determined by 300 MHz NMR.

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