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Oxygenative Radical Cyclization with Molecular Oxygen

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Abstract: 5-*exo* radical cyclization of olefinic iodides can be carried out under classical reductive tin hydride conditions in the presence of molecular oxygen to give high yields of cyclized alcohols.

Radical cyclization is a well established methodology for the formation of carbon-carbon bonds and the efficient elaboration of cyclic and polycyclic compounds.[1] In most cases, the last atom transfer is the reduction of the cyclized radical with an hydride donor to give the alkane (figure 1).

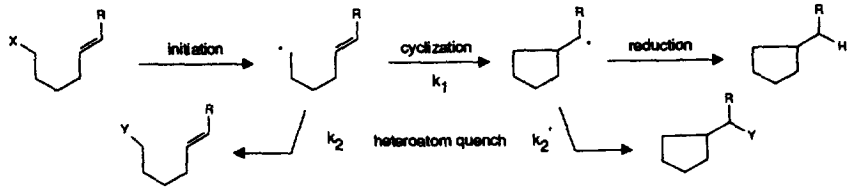
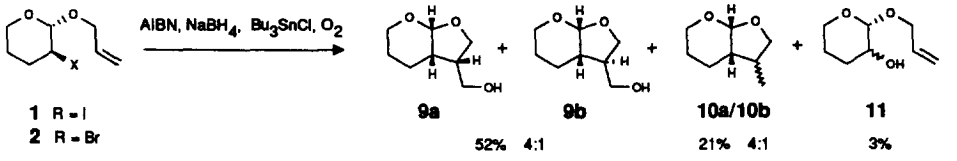


Figure 1

Notable exceptions are the atom transfer method[2] and the decomposition of alkylcobalt complexes related to vitamin B_{12} in presence of radical trapping agents.[3] Some other methodologies have also been described to obtain the same result.[4] Development of reliable and practical methods for the functionalization of the cyclized radical would be a valuable asset in synthesis as they will introduce two functionalities (cycle and the new C-Y bond) at the expense of two (unsaturation and radical precursor group X). We report that 5-*exo*-radical cyclization of olefinic iodides in classical tin hydride conditions and in presence of molecular oxygen proceeds in high yield to the cyclized alcohols. Carbon-centered radical oxygenation is a well documented reaction and synthetic applications have been described with molecular oxygen[5] or nitroxyl radicals.[6] However, there are only very few reports of radical cyclizations followed by an oxygen quench.[5f,6a,6b,6e,7]

All starting materials, except compound **6**[8], were obtained in good yield by NBS or NIS-promoted iodo-alkoxylation of the corresponding double bond with the appropriate alcohol in methylene chloride or acetonitrile.[9] Treatment of the olefinic iodide **1** in refluxing ethanol with AIBN, sodium borohydride and a catalylic amount of tributyltin chloride[10] under a stream of dry air gave the cyclized alcohols **9a** and **9b** in 52% yield as a 4 to 1 mixture of diastereoisomers (scheme 1). Other identified products were the reduced cyclized compounds **10a** and **10b** (21%, same diastereoisomeric ratio as **9**) together with minor amounts of

starting material (3%) and alcohols **11** arising from the oxygenation of the uncyclized radical (3%).[5g] Under optimized conditions, the yield of **9** could be increased to 64%. Other results are summarized in Table 1.



Scheme 1

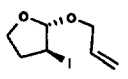
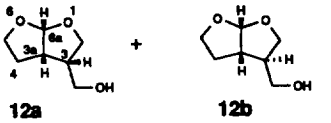
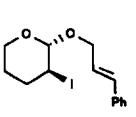
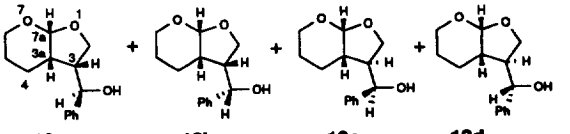
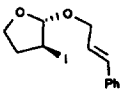
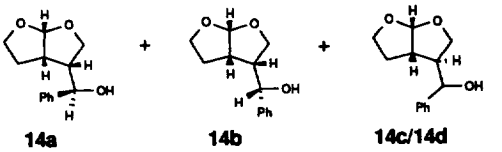
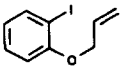
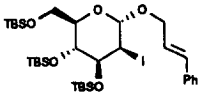
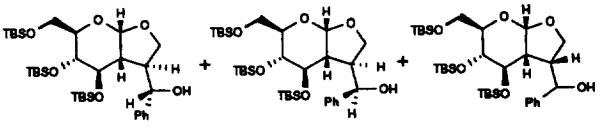
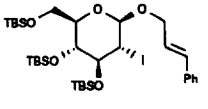
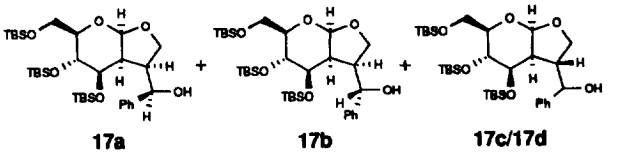
The reaction is general for 5-hexenyl iodides and gives good to excellent yields of cyclized alcohols. Bromide **2** was much less reactive than iodide **1** and gave only 25% of products **9a** and **9b** after 14 hours whereas running the reaction at higher temperature in refluxing 1-propanol gave only a marginal improvement in the yield with considerable amounts of recovered starting material.

The reaction can be run under stoichiometric tributyltin hydride conditions in toluene (procedure B, AIBN, Bu_3SnH, 80°C) or under the catalytic version developed by Corey[10] (procedure A, AIBN, 5-10% Bu_3SnCl, $NaBH_4$, EtOH, reflux) with equally good results. In the former case, the hydride concentration must be kept low (slow addition of the tin reagent) in order to minimize the competitive reduction of the carbon-centered radicals, removal of the tin compounds was also more tedious. These drawbacks are circumvented in the catalytic case which could be run without any special precautions. Some minor selectivity differences were observed with substrate **7**. Use of pure oxygen instead of air gave consistently lower conversion and lower yields of products under otherwise identical conditions. It is worth noting that, in contrast with the examples of tributyltin hydride-mediated oxygenative radical cyclizations described by Nakamura,[5f] stabilization of the radicals and/or ultrasonic activation were not required and good yields of alcohols were obtained from unsubstituted allyl precursors under thermal conditions. As was already observed in the decomposition of alkyl-cobalt complexes under oxygen, product **15a** was contaminated with a small amount of the lower homolog **15b** which could arise from the fragmentation of an intermediate alkoxy radical.[3b]

Two important points need to be emphasized : first, use of less than stoichiometric quantities of radical initiator (AIBN) gave low yields and recovered starting material even after prolonged reaction time; second, the reaction could be run without any tin compound, albeit with reduced efficiency. Thus, treatment of **5** with 1.5 eq of AIBN and 6 eq. of $NaBH_4$ in refluxing ethanol gave a 52% yield of products **14** after 8 hours in the same diastereoisomeric ratio as above, oxygenation of **6** with 2.5 eq. of AIBN and 3.7 eq. of $NaBH_4$ gave **15a** in 18% yield. The ability of azo compounds to initiate radical reactions in the absence of any tin has been briefly mentioned.[11]

Assignment of the configuration of the products was based on extensive nOe measurements on the individual purified isomers and comparison with known and related compounds.[12,13] The configuration of the exocyclic stereocenter in products **13**, **14**, **16** and **17** was correlated with the observed shielding effect of the phenyl ring on the chemical shifts of H-2[14] and H-3a. All experimental determinations were in good agreement with the known stereochemical preferences for these reactions[15] with a favored chair conformation for the transition state. Despite some conformational flexibility due to severe steric crowding from the three bulky silyl groups around the ring ($^3J_{H\text{-}4,H\text{-}5}$ = 7 Hz, $^3J_{H\text{-}5,H\text{-}6}$ = 7 Hz), the sugar-derived substrate **8** gave the 7a,3a-*cis* 7a,3-*trans* isomer predominantly in accord with the reported related examples.[13]

Table 1

Substrate	Procedure, Yield Selectivity	Products
1	a 64% 80/20	9a 9b
2	a 25% 80/20	9a 9b
 3	a 72% 94/6	 12a + 12b
 4	a 78% 44/22/17/17 b 64% 42/27/16/15	 13a + 13b + 13c + 13d
 5	a 69% 51/27/11/11	 14a + 14b + 14c/14d
 6	a 74% 85/15	 15a + 15b
 7	a 71% 46/28/16/10 b 78% 56/28/9/5	 16a + 16b + 16c/16d
 8	a 84% 53/28/12/7	 17a + 17b + 17c/17d

a and b refer to procedure A and B respectively (see text).

Reaction of carbon-centered radicals with molecular oxygen is very fast and thought to be almost diffusion-controled with k_2 and k'_2 values in the order of 2 10^9 mol^{-1}. s^{-1} at 298K (figure 1).[16] Direct oxygenation of the 5-hexenyl radical to 5-hexenol has been reported to proceed in 64% yield with less than 1% of cyclized material,[17] which is in sharp contrast with our results and other examples.[5f] Examination of the kinetic data for these radical cyclizations[15b] clearly shows that for the 5-hexenyl radical under pure oxygen at

room temperature (k_1 = 2.5 10^5 s^{-1}, the concentration of dissolved oxygen is about 10^{-2} mol. l^{-1} [18]) $k_2[O_2]_{diss}/k_1 >> 1$ and direct oxygenation is obtained. However, all successfull cases of oxygenative radical cyclizations, including ours, involve fast cyclization of the radicals ($k_1 \geq 10^7$ s^{-1} at 298K) and use of air instead of pure oxygen. If we take as an upper limit the approximative value of 10^{-3} mol. l^{-1} for the concentration of dissolved oxygen in refluxing ethanol under air, the minimum $k_1/k_2[O_{2diss}]$ ratio is 5 and cyclization is favored over the direct quench.

We have shown that the 5-*exo* radical cyclization/oxygenation sequence reaction could be efficiently run with molecular oxygen as the radical trap under slightly modified classical tin hydride conditions. High yields of cyclized alcohols are obtained in a single step from olefinic iodides. We are currently working on synthetic applications and the intriguing mechanistic aspects of this reaction.

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