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# Radical Cyclizations of Oxime Ethers Connected with Aldehydes or Ketones : A New Entry to Cyclic Amino Alcohols

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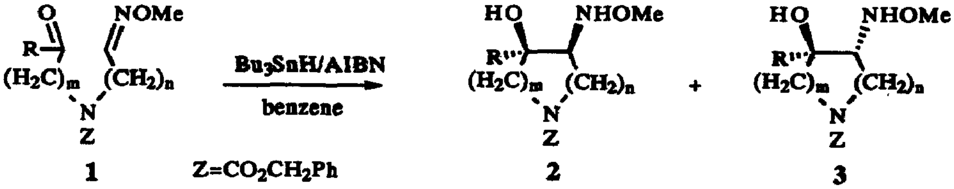
***Abstract:*** Oxime ethers connected by a tether to aldehydes or ketones efficiently cyclize in a free radical cyclization which is mediated by tributyltin hydride and provide a new entry to the cyclic amino alcohols.

Free radical cyclization has been an important tool for the construction of various types of cyclic compounds including biologically active natural products and medicinals.[1] There have been several examples involving radical cyclizations of olefins and alkynes having aldehydes or ketones in the presence of tributyltin hydride.[2] We now report the first example of tributyltin hydride-induced cyclization of oxime ethers[3] which are intramolecularly connected with aldehydes or ketones. The newly found radical cyclization provides a synthetically useful method for the construction of cyclic amino alcohols widely found in biologically active natural products such as amino sugars, amino cyclitols, and sphingolipids.

A 0.45 mol $dm^{-3}$ solution containing tributyltin hydride (2 equiv.) and AIBN (0.2 equiv.) in benzene (6 ml) was added dropwise over 2 h to a 0.13 mol $dm^{-3}$ solution of the oxime ether (**1a**,[4] 344 mg, 1 equiv.) in boiling benzene (10 ml) while stirring under nitrogen. The solution was then refluxed for a further 3 h and the solvent was removed *in vacuo*. The resulting residue was purified by medium pressure column chromatography to give the cyclized products **2a** and **3a**. Several other examples of the cyclization are shown in Table 1. The radical cyclizations proceeded very smoothly to give five to seven membered cyclic amino alcohols in good yields in which *trans*-isomers **3** were obtained as a major product. The newly found radical cyclization was extended to the oxime ether having terminal ketone **1e** which gave effectively two cyclic amino alcohols **2e** and **3e**. Radical cyclizations in the formations of seven membered products **2d** and **3d** and tertiary alcohols **2e** and **3e** proceeded slowly to recover the starting compounds in 35-46% yields. The stereostructures of products **2** and **3** were firmly established by the chemical conversions involving the formation of the corresponding cyclic ketals and oxazolidinones in the *cis*-isomers **2** except **2d** and **3d**, both of which gave the corresponding acetonides.

**Table 1.** Intramolecular Radical Cyclization of Oxime Ethers with Aldehydes or Ketones



| Substrate | R | m | n | Reaction Time (hr) | Ratio **2**:**3** | Combined Yields (%) |
|---|---|---|---|---|---|---|
| **1a** | H | 1 | 1 | 5 | 30:70 | 54 |
| **1b** | H | 2 | 1 | 6 | 39:61 | 62 |
| **1c** | H | 1 | 2 | 8 | 20:80 | 70 |
| **1d** | H | 3 | 1 | 9 | (32:68)[a] | 44 (70)[b] |
| **1e** | Me | 1 | 1 | 9 | 21:79 | 52 |

All cyclized products gave IR, $^1$H NMR, mass spectrum and accurate mass data consistent with the structures shown; Ratios were determined on the isolated yields respectively; [a] Stereochemistries of **2d** and **3d** have not been established; [b] Yield when 1 equiv. of AIBN was used.

In conclusion, a general method for the intramolecular cyclization of oxime ethers tethered to the carbonyl groups has been developed. The application of these methods to the synthesis of the biologically active natural products is in progress.

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4. Starting substrates **1** were readily prepared by oxidation of the corresponding oxime ethers having hydroxyl groups.

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