RADICAL CYCLIZATIONS OF VINYLOGOUS SYSTEMS INVOLVING OXIME ETHERS CONNECTED WITH CARBONYL GROUPS

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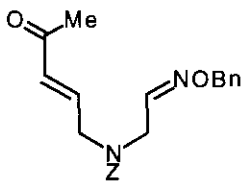
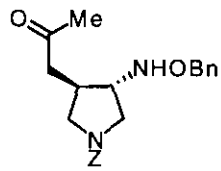
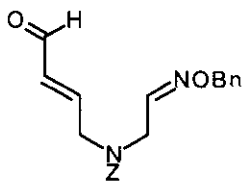
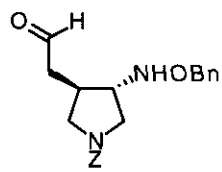
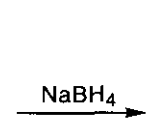
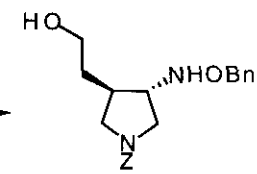
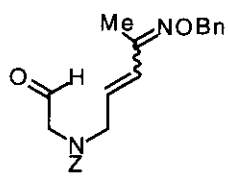
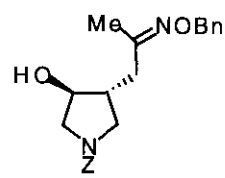
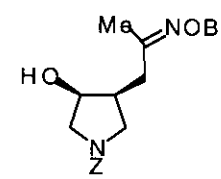
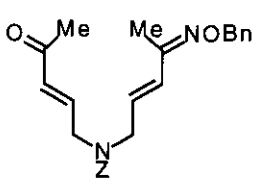
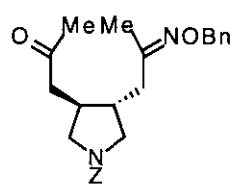
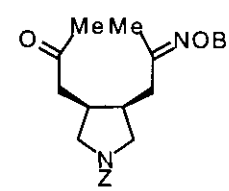
Abstract - Stannyl radical addition-cyclization of the isolated oxime ethers or α,β-unsaturated oxime ethers connected by a tether to α,β-unsaturated aldehydes or ketones provides a new entry to the adjacently functionalized heterocycles.

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] Among hitherto known radical cyclizations, radical addition-cyclization is also a potential synthetic reaction for the construction of functionalized cyclic compounds because the starting substrates are readily available and the products are appropriately functionalized by hetero-atoms.[2] There have been several examples of stannyl radical addition-cyclization of the carbonyl groups connected with another multiple bond such as alkene,[3] alkyne,[4] carbonyl[5] and carbon-nitrogen bonds.[6] We have recently reported a novel stannyl radical addition-cyclization of oxime ethers connected with the carbonyl group employing the oxime ether group as an excellent radical acceptor.

As a continuation of our studies on the development of a general and practical synthetic method for the functionalized heterocycles,[7] we have systematically investigated stannyl radical addition-cyclization of the vinylogous systems involving an oxime ether connected with a carbonyl group. Expectedly cyclized products would be not only useful precursors for the synthesis of biologically active compounds but also structural elements in a variety of more complex molecules.[8] There are three types of the substrates depending upon the number and the position of the double bonds conjugated with either each or both of two functional groups, oxime ether and carbonyl groups.

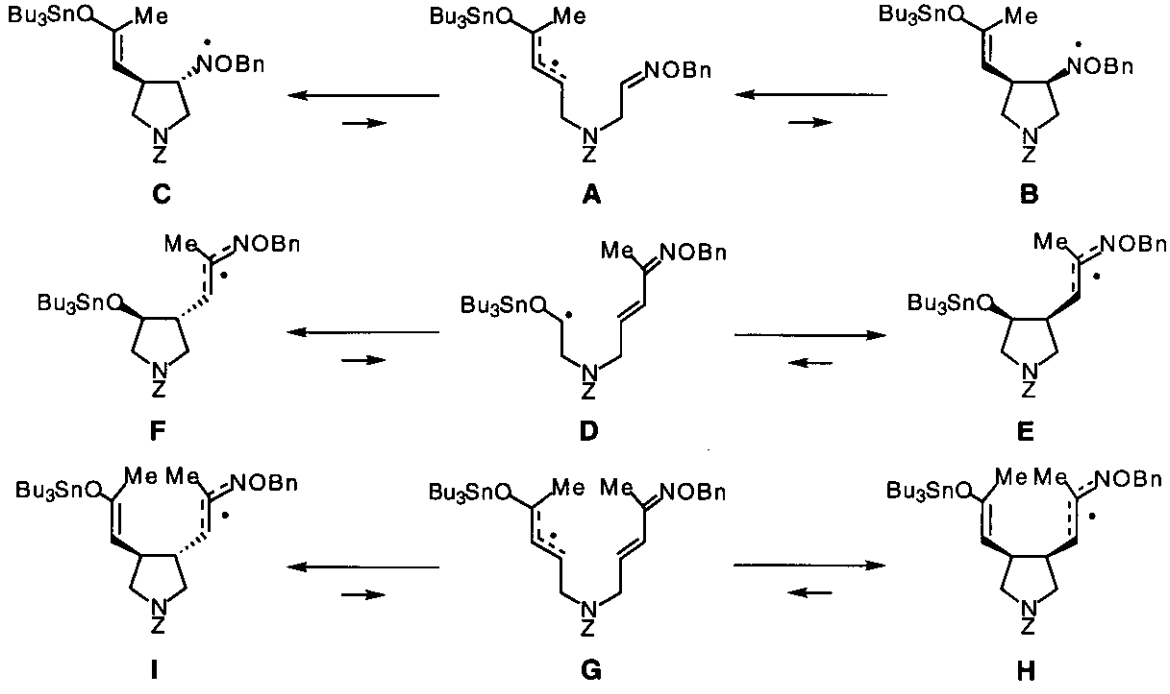
We first investigated the radical cyclization of oxime ether (**1**) connected with α,β-unsaturated ketone. Treatment of the oxime ether (**1**) with Bu_3SnH (2 equiv.) and AIBN (0.2 equiv.) in refluxing benzene (0.1 M) for 1.5 h under nitrogen underwent smooth cyclization to afford five-membered *trans*-product (**2**)[9] as a single isomer in 58% yield after medium pressure column chromatography (Table 1, Entry 1). Radical addition-cyclization of the relatively unstable oxime ether (**3**) connected with α,β-unsaturated formyl group proceeded to afford five-membered unstable *trans*-product (**4**) which was characterized as its corresponding stable alcohol (**5**)[9] prepared by the $NaBH_4$ reduction. Thus it is found that the radical cyclization of oxime ethers connected with α,β-unsaturated carbonyl group gave stereoselectively five-membered *trans*-pyrrolidines containing the γ-aminocarbonyl group.

Table 1. Stannyl Radical Addition-Cyclization of Oxime Ethers

Entry	Substrate	Products: Yield % (ratio)
1	 **1**	 **2** 58%
2	 **3**	 **4**   **5** 49%
3	 *E*-olefin **6** 37% (1 : 1.5) *Z*-olefin **6** 47% (1 : 1)	 **7** +  **8**
4	 **9**	 **10** 59% (8 : +  **11** 5)

We then investigated the radical addition-cyclization of α,β-unsaturated oxime ethers (**6**) connected with the formyl group which were prepared as an *E*- and *Z*-olefinic isomers. Under the same reaction condition as above, radical addition-cyclizations of both *E*- and *Z*-olefinic oxime ethers (**6**) proceeded slowly (3 h) compared with the above-mentioned substrates (**1**) and (**3**) to give a mixture of five-membered *trans*- and *cis*-stereoisomers (**7**)[9] and (**8**)[9] in 37-47% combined yields. Thus in the radical cyclization of α,β-unsaturated oxime ethers (**6**), the geometry of the carbon-carbon double bond in the substrates seems to influence subtly on the reactivity and stereoselectivity leading to the formation of five-membered *trans*- and *cis*-products.

Finally we investigated the radical addition-cyclization of α,β-unsaturated oxime ether (**9**) connected with α,β-unsaturated carbonyl group thus having two conjugated double bonds. Under the same reaction condition as above, the reaction of (**9**) proceeded more slowly (5 h) than those of (**1**), (**3**), and (**6**) to give an 8 : 5 mixture of five-membered *trans*-(**10**)[9] and *cis*-(**11**)[9] in 59% combined yield.



From the systematic studies on stannyl radical addition-cyclizations of three types of oxime ethers (**1** and **3**), (**6**), and (**9**), we propose the possible reaction pathways as follows. In the oxime ethers (**1**) and (**3**) connected with α,β-unsaturated carbonyl group, a stannyl radical adds to an oxygen atom of α,β-unsaturated carbonyl group to form allylic *O*-stannyl ketyl radical (**A**)[10] which is intramolecularly trapped with the oxime ether group as a radical acceptor. The cyclized *cis*-intermediate (**B**) would be sterically less stable than the *trans*-intermediate (**C**). Therefore even if the *cis*-intermediate (**B**) would be transiently formed, it would return to the ring opened stable allylic ketyl radical (**A**) which would be equilibrated with sterically stable *trans*-intermediate (**C**). The stable *trans*-intermediate (**C**) was finally trapped with Bu_3SnH to give the respective *trans*-products (**2**) and (**4**) as a sole product. In α,β-unsaturated oxime ethers (**6**), both *cis*- and *trans*-cyclized intermediates (**E**) and (**F**) are stabilized by the allylic alkoxyaminyl radical and therefore stability difference between both intermediates (**E**) and (**F**) is not so large that they are trapped with Bu_3SnH to give a mixture of *cis*- and *trans*-products. In other words, there would be no equilibration between two intermediates (**E**) and (**F**) *via* a ring opened ketyl radical (**D**). Radical addition-cyclization of (**9**) bearing two conjugated systems would proceed similarly to the second one. Relatively stable allylic ketyl radical (**G**) would attack slowly at the conjugated oxime ether which would be less reactive radical acceptor to form a mixture of *cis*- and *trans*-allylic alkoxyaminyl radicals (**H**) and (**I**). The radicals (**H**) and (**I**) were reduced to afford a mixture of two five-membered products.

In conclusion, our systematic investigation on the stannyl radical addition-cyclization of vinylogous systems involving oxime ethers connected with the carbonyl group established a novel synthetic method for the bifunctionalized pyrrolidines. The application of the method to the synthesis of biologically active natural products is in progress.

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9. The stereostructures of the cyclized products (**2**), (**5**), (**7**), and (**8**) were deduced on the basis of their ^{1}H-NMR and NOESY spectra. (**10**) and (**11**) were characterized by not only ^{1}H-NMR spectra but also the chemical shifts of the ^{13}C-NMR signals[11] due to two carbons at the 3 and 4-positions of the corresponding bismethyl ketone derivatives which were readily prepared by treatment of (**10**) and (**11**) with *p*-TsOH and HCHO.
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