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Hydroximate as a Synthetically Useful Functional Group: A Novel Synthesis of Lactones Using Hydroximates as a Tether

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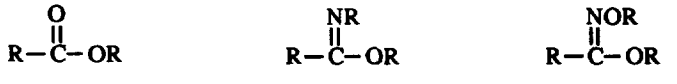
Abstract: Hydroximate has proved to be a potential functional group by realizing the radical cyclization of the dienes connected with the hydroximates **4** and **10** followed by conversion of the resulting cyclic hydroximates **5**, **6**, **11**, and **12** to lactones **13** and **14**.

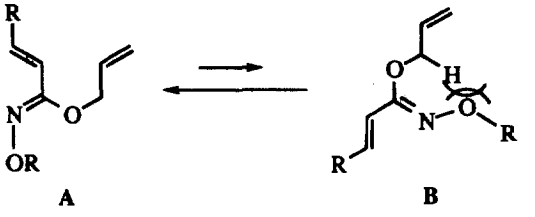
Ester **1** is one of the most important functional groups in organic synthesis. Furthermore, the imidate **2**, an imino analogue of esters, has recently received much attention due to their interesting reactivities.[1] In contrast, little is known about the chemistry of hydroximate **3**, *N*-alkoxyimidate which is expected to be a reactive synthon based on a combination of two types of heteroatoms and existence of two geometrical *E*- and *Z*-isomers in the hydroximates.[2] We now report the first example of radical cyclization of the dienes[3] connected with the hydroximates which are indispensable to cyclization and lactone synthesis. The corresponding dienes connected with ester did not undergo the radical cyclization. The newly found radical cyclization of the hydroximates provides an alternative method for the construction of butyrolactones[4] which were effectively derived by hydrolysis.



1 **2** **3**

Expecting that, contrary to the esters, *Z*-*O*-alkylhydroximates would exist in a conformer **A** preferable to intramolecular cyclization over the less favored conformer **B** due to the steric repulsion between the substituents on nitrogen and oxygen atoms in the conformer **B**, we first investigated the radical cyclization of allyl *Z*-*O*-

methylcinnamoylhydroximate **4a**[5] in the presence of thiophenol and AIBN (Table 1, entry 1). A solution containing thiophenol (1 equiv.) and AIBN (0.5 equiv.) in benzene was added dropwise by a syringe pump over 2 h to a solution of **4a** in boiling benzene while stirring under nitrogen. The solution was then refluxed for further 1 h and the solvent was removed *in vacuo*. The resulting residue was purified by medium pressure column chromatography to give a 1.8:1 mixture of the *cis*-**5a**[6] and *trans*-cyclized products **6a**[6] in 82% combined yield.



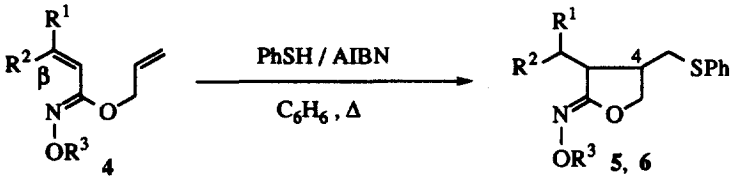
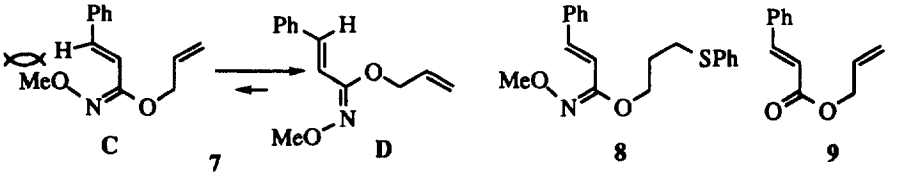


Table 1. Thiyl Radical Addition-Cyclization of Hydroximates **4a-d**

Entry	Substrate	R^1	R^2	R^3	Yield (%)	Ratio *cis*-**5** : *trans*-**6**
1	**4a**	Ph	H	Me	82	1.8 : 1.0
2	**4b**	Me	Me	Me	80	1.7 : 1.0
3	**4c**	Ph	H	Bn	94	1.8 : 1.0
4	**4d**	COOEt	H	Bn	78	0.8 : 1.0

Under the same reaction condition, *E*-isomer **7**[5] and the corresponding ester **9** did not give the cyclized products and the substrates were recovered though *E*-hydroximate **7** gave an adduct **8** in 3% yield. The fact that *E-O*-alkylhydroximate **7** did not cyclize would be explained as follows. *E*-isomer **7** would exist in a stable conformer **D** which is unfavorable to intramolecular cyclization. Another conformer **C** is preferable to cyclization but has the steric repulsion between methoxy group and olefinic hydrogen.



The substituent effect of the thiyl radical addition-cyclization was then investigated in order to establish the scope and limitations as shown in Table 1. The hydroximates **4b-d**[5] with substituents at β-position of the unsaturated hydroximate group gave the desired cyclic hydroximates **5b-d**[6] and **6b-d**[6] in good yields which possess the phenylthiomethyl group at 4-position. Alternatively, the absence of the substituents at β-position in the unsaturated hydroximates **10a-d**[5] influenced markedly the regioselectivity of the addition of the phenylthiyl radical, resulting in the exclusive formation of the 3-phenylthiomethyl products **11a-d**[6] and **12a-d**[6] as shown in Table 2. These results suggest that the dienes connected with *Z*-hydroximates undergo smooth 5-*exo*-*trig* type of radical cyclization though its regiochemistry depends on the substituents attached to the π-bond.

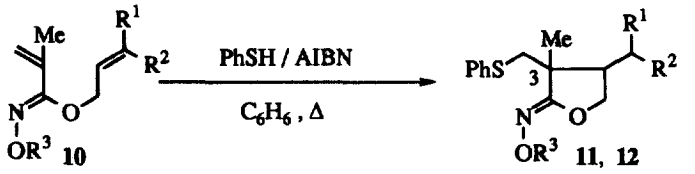
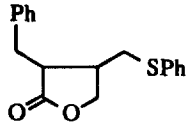


Table 2. Thiyl Radical Addition-Cyclization of Hydroximates **10a-d**

Entry	Substrate	R^1	R^2	R^3	Yield (%)	Ratio *cis*-**11** : *trans*-**12**
1	**10a**	Ph	H	Me	78	1.7 : 1.0
2	**10b**	Me	H	Me	56	1.7 : 1.0
3	**10c**	Me	Me	Me	58	1.1 : 1.0
4	**10d**	COOEt	H	Me	49	1.3 : 1.0

Conversion of the cyclic hydroximates to the lactones was very readily achieved as follows. To our knowledge, there is no example of the transformation of the hydroximates to the esters or lactones. Hydrolysis of *cis*-**5a** and *trans*-**6a** with 10% HCl or paraformaldehyde and Amberlyst[7] gave the desired *cis*- and *trans*-lactones **13** in 93-95 % or 50-60 % yield. Similarly, upon treatment with 10% HCl, *cis*-**11a** and *trans*-**12a** having 3-phenylthiomethyl group gave *cis*- and *trans*-lactones **14** in 79-95 % yield.



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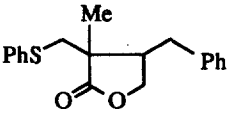

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In conclusion, we have now established a novel synthetic route for lactones *via* a combination of thiyl radical addition-cyclization and the subsequent hydrolysis of the hydroximates which have proved to be a new and promising functional group in the synthetic organic chemistry. The applications of these methods to the synthesis of the biologically active natural products are in progress.

ACKNOWLEDGEMENTS We wish to thank the Ministry of Education, Science, and Culture (Japan) and to the Science Research Promotion Fund of the Japan Private School Promotion Foundation for research grants.

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6. Structures of the stereoisomeric hydroximates **5a-d** and **6a-d** were established by irreversible isomerization of *cis*-hydroximates **5a-d** to *trans*-isomers **6a-d** with sodium ethoxide and single-crystal X-ray analysis of *cis*-**5a**. Stereostructures of the cyclic hydroximates **11a-d** and **12a-d** were established by their NMR spectra including NOESY spectra. Crystal data of *cis*-**5a**: $C_{19}H_{21}NO_2S$, space group P_{bca} with a=18.131 (3), b= 26.611 (2), c= 14.575 (1) Å, V= 7032.4 (1.5) Å^3. Final R value was 0.060 for 5980 reflections.
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