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Stereoselective Synthesis of Acyltetrahydrofurans *via* Bicyclic Oxazines

Hyo Won Lee

Department of Chemistry, Chungbuk National University, Cheongju 361-763, Korea

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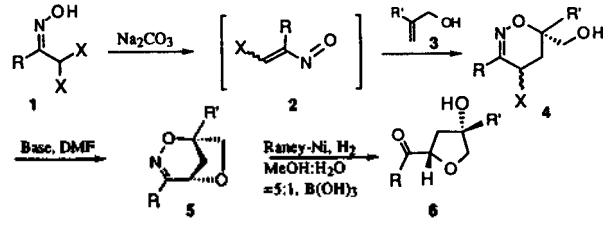
It is useful to use a heterocycle as a precursor or an intermediate for functionalization or structural transformation of organic compounds. Monohalo-substituted oxazines can be utilized for the preparation of tetrahydrofurans. Herein we would like to report the utilization of α,α-dihalooximes in the preparation of *cis*-5-acyltetrahydrofuran-3-ols *via* 4-halo-5,6-dihydro-4*H*-[1,2]oxazines.

It has been known that hetero-Diels-Alder reaction of *in-situ* generated nitrosoalkenes from a-halooximes with alkenes provides dihydro-4*H*-oxazines.[1,2] The attachment of a halogen atom at the 4 position of oxazine with 6-hydroxymethyl can lead to a tetrahydrofuranyl ring *via* intramolecular nucleophilic substitution of the halogen atom by hydroxy group. The reductive cleavage at N-O bond of oxazine ring yields the *cis*-2-acyltetrahydrofuran-5-ol.

In our synthetic plan α,α-dihalooximes **1** were taken to provide monohalo-substituted oxazine derivatives. (Scheme 1) Accordingly dihaloketones were treated with hydroxylamine hydrochloride in MeOH at room temperature for 2-4 days to provide **1**. Halovinylnitroso compounds **2**, which were *in situ* generated by the reaction of **1** with Na_2CO_3, underwent [4+2] cycloaddition with allylic alcohols **3** to give isomeric mixture of 5,6-dihydro-4-halo-1,2-oxazines **4**.[3] However, when these oxazines were treated with a base such as NaH or KH, 2,6-dioxa-3-azabicyclo[3.2.1]oct-3-enes **5** were obtained. The rationale for this stereoselectivity is that when a mixture of two halo isomers **4** was reacted under the basic condition, the equilibrium shifted toward thermodynamically more stable **4a**, which was then replaced by the pending hydroxyl group to furnish the bicyclic product **5**.

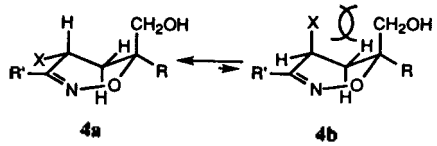


Scheme 1. Reaction Pathway to *cis*-2-Acylfuran-5-ol.

Table 1. Conversion of Oxime **1** to Ketone **6** *via* Oxazine Derivatives **4** and **5**

Entry	Oximes 1		Oxazines 4 Alcohols 3 (% Yield)	Bicyclic Oxazines 5 (% Yield)	Ketones 6 (% Yield)
1[a]	R=Me, X=Cl	R'=H	25	47	75
2[a]	R=Me, X=Cl	R'=Me	45	62	91
3	R=Ph, X=Br	R'=H	69	73	78
4	R=Ph, X=Br	R'=Me	76	91	73
5	R=*p*-ClPh, X=Br	R'=H	81	75	85
6	R=*p*-ClPh, X=Br	R'=Me	98	76	92

[a] KH was used to generate bicyclic oxazine **5**, otherwise NaH was used.



4a **4b**

The reductive cleavage of N-O bond of bicyclic oxazines **5** with Raney Nickel (methanol : H_2O=5 : 1) gave stereoselectively acyltetrahydrofurans **6** in good yield.[4] The results were shown in Table 1.

Currently synthetic applications of this methodology for the preparation of other medium size cyclic ethers are in progress.

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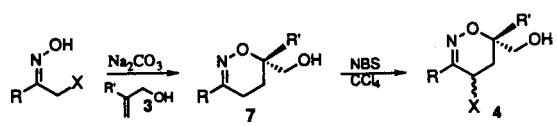
3. Compounds **7** can be brominated at 4-position with NBS to provide compounds **4**. However, the utilization of dibromooximes gave better yields of the oxazines.



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