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Vinylogous Sulfonates as Radical Acceptors for the Stereoselective Synthesis of Cyclic Ethers

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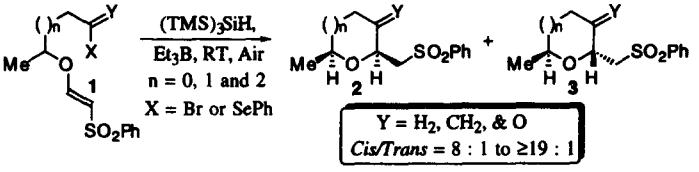
Abstract: *Treatment of the* E*-vinylogous sulfonates* ***1a-g*** *with tris(trimethylsilyl)silane and triethylborane, in the presence of air, at room temperature furnished the cyclic ethers* ***2/3a-g*** *in 34-99% yield with ≥8 : 1* cis*-diastereoselectivity.* © 1997 Elsevier Science Ltd.

Cyclic ether containing natural products represent both architecturally challenging and biologically important molecules, that have stimulated the development of an array of methods for their stereocontrolled syntheses.[1,2] Methods that utilize radicals as reactive intermediates have gained considerable prominence in recent times, primarily due to the high degree of stereocontrol that can often be achieved and the possibility of also forming several new carbon-carbon bonds in a single transformation.[3-5] In a program directed at the synthesis of cyclic ether containing natural products, we decided to investigate the merit of vinylogous sulfonates for a series of intramolecular radical cyclizations. Vinylogous sulfonates would provide an attractive alternative to the vinylogous carbonates previously examined,[5a-c] by allowing alternative modes of functionalization. In this paper, we describe a series of novel intramolecular additions of acyl, alkyl and vinyl radicals to vinylogous sulfonates (**Scheme 1**), the results of which are summarized in **Table 1**.



Scheme 1

Tetrahydrofuran construction: Treatment of the vinylogous sulfonates **1a-b**[6,7] with tris(trimethylsilyl)silane[8] and triethylborane at room temperature, in the presence of air, furnished the 2,5-disubstituted tetrahydrofurans **2/3a-b** in 87-99% yield, with excellent *cis*-diastereoselectivity (Entries 1-2). The stereochemical course of these cyclizations can be rationalized using the *Beckwith Transition State Model*, which has been used to predict the outcome of 5-hexenyl type radical cyclizations.[9,10]

Tetrahydropyran construction: The synthesis of tetrahydropyrans was initiated by treating the vinylogous sulfonates **1c-e**[6,7] under analogous conditions to those described above, to afford the 2,6-disubstituted tetrahydropyran-3-ones **2c-e** in excellent yield (Entries 3-5). The modest level of diastereocontrol obtained in the 6-*exo*-trigonal acyl radical cyclization is comparable to that observed with vinylogous carbonates under analogous conditions.[5b] The diastereomeric mixture **2e/3e** could however be equilibrated to the thermodynamically more stable diastereoisomer **2e**, using a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene. The modest diastereocontrol in this particular cyclization may be circumvented by employing the *Z*-vinylogous sulfonate, as exemplified in our recent approach to the tetrahydropyran portion of the antitumor agent mucocin.[5d]

Table 1: Intramolecular Radical Cyclizations of the *E*-Vinylogous Sulfonates **1a-g**[6,7]

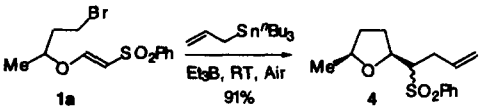
Entry	Vinylogous Sulfonate **1**[a]			Conc.[b]	Ratio of **2** : **3**[c,d]	Yield (%)[e]
1	**1a**	n = 0	X = Br Y = H_2	0.02 M	≥19 : 1	99
2	**1b**	n = 0	X = SePh Y = O	"	17 : 1	87
3	**1c**	n = 1	X = Br Y = H_2	0.01 M	≥19 : 1	90
4	**1d**	n = 1	X = Br Y = CH_2	"	≥19 : 1	96
5	**1e**	n = 1	X = SePh Y = O	"	8 : 1	83
6	**1f**	n = 2	X = Br Y = H_2	0.005 M	≥19 : 1	34
7	**1g**	n = 2	X = SePh Y = O	"	17 : 1	63

[a] All the cyclizations were carried out on a 0.3 mmol reaction scale. [b] $(TMS)_3SiH$, Et_3B, PhH, RT. [c] Ratios of diastereoisomers determined by 400 MHz ^{1}H-NMR integration. [d] All new compounds exhibited spectroscopic (IR, ^{1}H and ^{13}NMR) and analytical (HRMS) data in accord with the assigned structure. [e] Isolated yields.

Oxepine construction: The synthesis of 2,7-disubstituted oxepines **2/3f-g** was also investigated. Treatment of the vinylogous sulfonates **1f-g**[6,7] with tris(trimethylsilyl)silane[8] and triethylborane, in the presence of air, at room temperature afforded the 2,7-disubstituted oxepines **2/3f-g** in 34-63% yield, with very good diastereoselectivity (Entries 6-7). Interestingly, in the acyl radical cyclization the predominant byproduct was the aldehyde, which is presumably formed from the reduction of the acyl radical. The aldehyde byproduct can then, in principle, be reoxidized and converted to the acyl selenide **1g**, and be resubmitted to the cyclization reaction. This clearly illustrates how the low temperature reaction conditions suppress decarbonylation,[5b] which was the predominant pathway at

higher temperature (*ca.* 80 °C). It is evident from the yield that the vinylogous sulfonate is not as efficient an acceptor as the vinylogous carbonate for this particular ring size, especially the alkyl radical.

The Keck allylation protocol[11] was also applied to the 5-exo trigonal cyclization of **1a**, in which the tandem formation of two new carbon-carbon bonds was achieved. Thus, treatment of the alkyl halide **1a** with allyltributyltin and triethylborane at room temperature, in the presence of air, furnished the cyclic ether **4** in 91% yield, epimeric (1 : 1) at the phenylsulfonyl group (**Scheme 2**).[10] This transformation is likely to provide a useful method for the homologation of these systems, and will be particularly attractive for the introduction of side chains in a single transformation, which will avoid a more standard multi-step homologation sequence.



1a 4

Scheme 2

In conclusion, we have demonstrated the first examples of the intramolecular addition of acyl, alkyl and vinyl radicals to *E*-vinylogous sulfonates for the efficient and stereoselective synthesis of cyclic ethers. The excellent regiochemical control in the cyclization reactions described herein is presumably the result of the intramolecular addition of nucleophilic radicals to the LUMO of the vinylogous sulfonate.[12] The stereochemical outcome was confirmed by a series of NOE experiments, and is presumably the result of the favored transition state (n = 0, 1 and 2) having the alkyl substituent pseudo-equatorial with the vinyl ether *s-trans*, presumably to alleviate $A^{1,3}$ allylic strain in the transition state leading to the product.[5]

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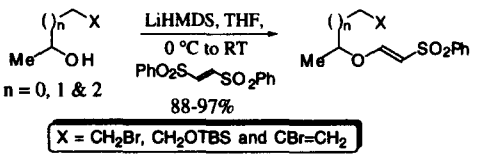
6. The *E*-vinylogous sulfonates **1a-g** were prepared in a stereospecific manner using the protocol outlined below. Treatment of the various secondary alcohols with LiHMDS at 0 °C followed by *E*-bis(phenylsulfonyl)-1,2-ethylene furnished the *E*-vinylogous sulfonates in excellent yield.[7]



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