Phenylselenoetherification of Some Δ^4-Alkenols Facilitated by Pyridine and Some Lewis Acids

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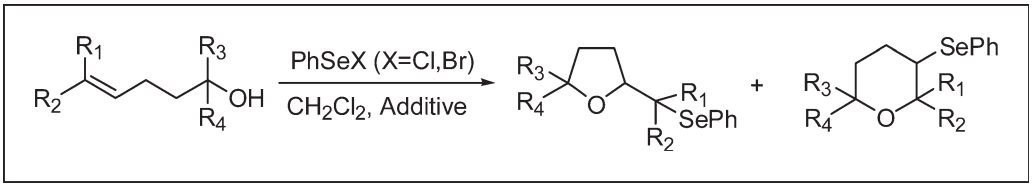

Studies on the phenylselenoetherification of some Δ^4-alkenols in the presence of pyridine and some Lewis acids are described. All alkenols underwent intramolecular cyclization yielding corresponding tetrahydrofuran or tetrahydropyran derivatives. Yield and diastereomeric ratio of the cyclic products depend on counterion of selenylating reagent used. We found that external additives, such as pyridine and some Lewis acids coordinating to the electrophilic and/or nucleophilic species are used to control the course of cyclizations with high degrees of efficiency and improve the level of stereoinduction.

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INTRODUCTION

Cyclization of unsaturated alcohols leading to cyclic ethers is well documented in a literature as convenient pathways in the synthesis of natural products and related compounds [1].

Substituted tetrahydrofuran and tetrahydropyran rings are common in many natural products and play important role as building blocks for the synthesis of various biologically active organic target molecules [2]. Stereoselective synthesis [3] of substituted cyclic ethers is important since cyclic ether units are frequently found in polyether antibiotics [4], C-glycosides [5], and polyene mycotoxins [6]. A number of these compounds exhibit remarkable antibiotic [4], neurotoxic [7], antiviral [8], and cytotoxic [9] effects, which have opened perspective for selected clinical applications [10]. This circumstance has brought about a growing demand for cyclic ethers in general. Since their supply cannot be covered from natural sources alone, the invention of methods for stereoselectively constructing the tetrahydrofuran and tetrahydropyran nucleus from unsaturated alcohols has received considerable attention [11].

Among the various kinds of ring-forming reactions, those based on the reaction of an electrophilic reagent with an alkene holding a suitably positioned hydroxyl group are certainly very useful. The term of cycloetherification is generally used to describe this kind of process which can be promoted by several electrophilic reagents [12]. The increasing popularity gained in recent years by selenium reagents induced ring closure reactions [13]. Different electrophilic selenium reagents and a variety of reaction conditions have been used and recent reviews are highlighting the broad scope of this general process [14]. Scheme 1 illustrates the possible modes of cyclization depending on the relative position of hydroxyl group and the double bond in the starting alkene.

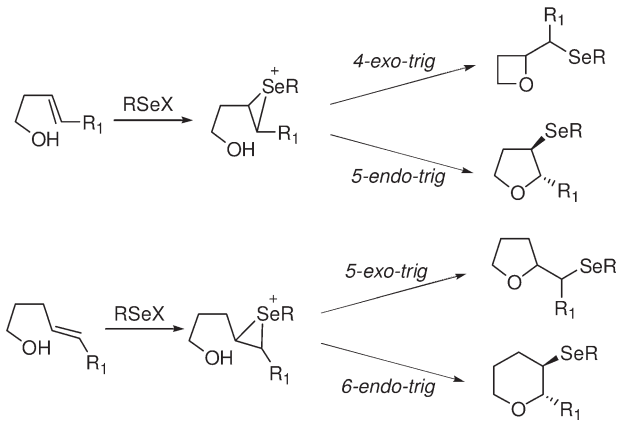
Outcome of this reaction is influenced by the nature of selenium reagent used, and the reactivity of the selenium electrophile also depends on the nature of counterion. Although standard conditions can be used for these cyclizations, the interactions between the selenium electrophile, counterion, the solvent, and the substrate are not fully understood, and we describe herein our recent investigations toward these cyclizations.

Lewis acids are widely used as catalysts and mediators in many organic reactions [15] and stereoselective synthesis [16]. However, PhSeCl in combination with equimolar amount of $ZnCl_2$ is known as strong chlorophenilselenilating reagent for olefins [17]. These findings prompt us to extend the use of Lewis acids to phenylselenoetherification of some Δ^4-alkenols. Now, we are interested in the behavior toward additives such as Lewis acids and pyridine in the reaction conditions to study reactivity and regiochemical and stereochemical outcome of the cyclization.

RESULTS AND DISSCUSION

In recent years, we have studied intramolecular cyclization of some Δ^4- and Δ^5-alkenols by means of phenylselenyl

Scheme 1



halides, PhSeX (X = Cl, Br) [18]. Intramolecular heterocyclization is the main reaction in the case of all investigated primary and secondary alkenols, while tertiary alkenols, under the same experimental conditions, are not converted into cyclic products at all by PhSeBr and in a small amount with PhSeCl. Although the additional products are expected, we have found that all investigated tertiary alkenols in the reaction with PhSeBr afforded γ- and δ-bromoalkanols in high yields [19].

Recently, we found that cyclizations of Δ^5-alkenols can be facilitated in the presence of pyridine, Ag_2O, and some Lewis acids as catalysts [18d]. In this article, we wish to present the extension of the method to Δ^4-alkenols. These alkenols envisage to the *5-exo* and/or *6-endo* cyclizations. Prompted by this fact, we considered it synthetically interested to study the influence of additives, pyridine, and some Lewis acids ($ZnCl_2$ and $FeCl_3$) on reactivity and regioselectivity and stereoselectivity in selenocyclization reaction.

The reactions are performed with two selenylating reagents, PhSeCl and PhSeBr, and equimolar amount of additives, in dichloromethane as solvent, at room temperature. All reactions proceeded to form five- and/or six-membered oxygen heterocycles bearing the phenylseleno moiety. The results of our investigation are shown in Scheme 2 and Table 1.

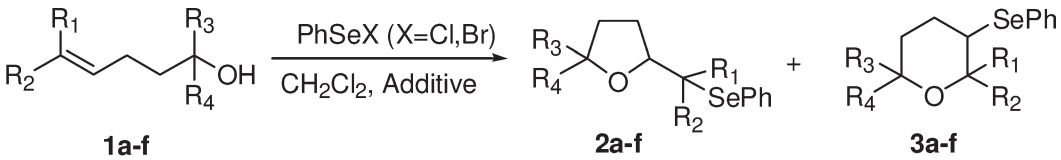
Primary **1a** and secondary **1c** alkenols gave expected tetrahydropyran-type cyclic ether products, while tertiary alkenols **1d–f** gave anti-Markovnikoff tetrahydrofuran-type products predominantly due to stereoelectronic effects.

Cyclization is facilitated by the presence of pyridine and Lewis acids. It became clear that phenylselenyl halides in combination with these additives usually gave rise to cleaner reactions and improved yields compared with phenylselenyl halides alone. Also, the additives increased the reaction rate dramatically. In the case of tertiary alkenols with larger substituents **1d**,**f**, the yields of products decreased regarding to the effects of steric hindrance. Depending on mechanism, this can indeed be expected. As it can be seen from Table 1, pyridine gave the best results, conversion to cyclic products was quantitative in all cases. It appears that the presence of pyridine is beneficial to the cyclizations process due to its basic properties. Function of external base was to neutralize hydrohalogenic acid generated on cyclizations. In the absence of external base, the halide counterion must fulfill this role and an undesired acid-promoted reaction was competitive. All additives could enhance the nucleophilicity of the hydroxyl group of the alkenol and also mediate the stabilization of oxonium ion intermediates.

Although phenylselenoetherification with nonhiral selenium reagents is generally known to give low stereoselectivity [20], very good results were obtained in the cyclizations of Δ^3-alkenols [21]. However, in all cases, stereoselectivity of the ring closure reaction was strongly influenced by the presence and the nature of allylic substituent in the starting alkenol.

In this context, we initiated our study of phenylselenoetherification of (*Z*)- and (*E*)-hex-4-en-1-ols **1b** under kinetic conditions using both selenium reagents and pyridine, in dichloromethane at temperature ranging from −78°C to room temperature. *cis*-Alcohol is envisage to facilitate the *5-exo*-favored cyclization, while *trans*-isomer facilitate the *6-endo*-unfavored cyclizations by the

Scheme 2



1a-f **2a-f** **3a-f**

a) $R_1=R_2=R_3=R_4=H$
b) $R_1=R_3=R_4=H$, $R_2=Me$
c) $R_1=R_2=R_3=Me$, $R_4=H$
d) $R_1=R_2=R_3=R_4=Me$
e) $R_1=R_2=R_3=Me$, $R_4=$ethenyl
f) $R_1=R_3=Me$, $R_2=$isoprenyl, $R_4=$ethenyl

Table 1

Phenylselenoetherification of Δ^4-Alkenols in the presence of pyridine, $ZnCl_2$, and $FeCl_3$.

	Yields (%) PhSeCl				Yields (%) PhSeBr			
Alkenol	No additives	Py	$FeCl_3$	$ZnCl_2$	No additives	Py	$FeCl_3$	$ZnCl_2$
1a	69	100	96	92	63	100	100	98
1b (*E*)	81	100	90	92	65	100	96	95
1b (*Z*)	72	100	98	96	75	100	99	98
1c	56	100	78	81	18	100	74	76
1d	37	100	71	75	0	100	60	62
1e	46	100	58	62	0	100	52	55
1f	23	100	53	58	0	100	48	52

Baldwin's rules, yielded regioselectively tetrahydrofurans **2b** (*threo* and *erythro*) and tetrahydropyrans **3b** (*trans* and *cis*), respectively (Scheme 3).

The experimental results, summarized in Table 2, show that more electrophilic PhSeCl was used to drive reaction more completely and maintain better stereoselectivity but the poorer electrophile, PhSeBr, gave reversal stereoselectivity. The results reveal the effect of reaction temperature, which drove the reaction further toward completion and better stereoselectivity. Superior results are obtained with pyridine. Conversion to cyclic ethers was quantitative with increased and reversal stereoselectivity regardless to reagent used. (*E*)-Hex-4-en-1-ol affords six-membered *cis*-izomer predominantly, while (*Z*)-hex-4-en-1-ol affords five-membered *erythro*-isomer as unique product.

We also studied the reactivity and stereoselectivity of these reactions in the presence of equimolar amount of some Lewis acids, which were considered as the perspective candidates. $ZnCl_2$, $FeCl_3$, and $AlCl_3$ were tested at room temperature. As it can be seen from the results obtained, Lewis acids also promoted cyclization process (Table 3). In all cases, reactions were high yielded. Diastereomeric ratio was improved and reversal stereoselectivity in the reactions with PhSeBr was not noticed. (*Z*)-Hex-4-en-1-ol affords five-membered *threo*-isomer, while (*E*)-hex-4-en-1-ol affords six-membered *trans*-isomer predominantly. In the presence of Lewis acids, reactivity of selenium electrophile is independent of nature of counterion.

All used additives can bound counter ion from reagent, increase electrophilicity of PhSe group, and eliminate X^- as a concurrent of hydroxyl group in cyclization step. They could also enhance the nucleophilicity of hydroxyl group of the alkenol and also mediate the stabilization of the oxonium ion intermediates.

In summary, we found that external additives, such as pyridine and Lewis acids coordinating to the electrophilic species are used to control the course of cyclizations with high degrees of efficiency and improve the level of stereoinduction. The course of cyclization can be directed as desired by the choice of the electrophile and the additives used in the reaction.

EXPERIMENTAL

Gas chromatography/mass spectrometry analyses were obtained with an Agilent Technologies instrument, model 6890 N with HP-5NS columns. ^1H and ^{13}C NMR spectra were run in $CDCl_3$ on Varian Gemini 200-MHz NMR spectrometer. IR spectra were obtained with Perkin-Elmer FTIR spectrophotometer model Spectrum one. Microanalyses were performed by ''Dornis and Colbe'' and found to be in good agreement with the calculated values. Thin layer chromatography was carried out on 0.25-mm E. Merck precoated silica gel plates (60F-254)

Scheme 3

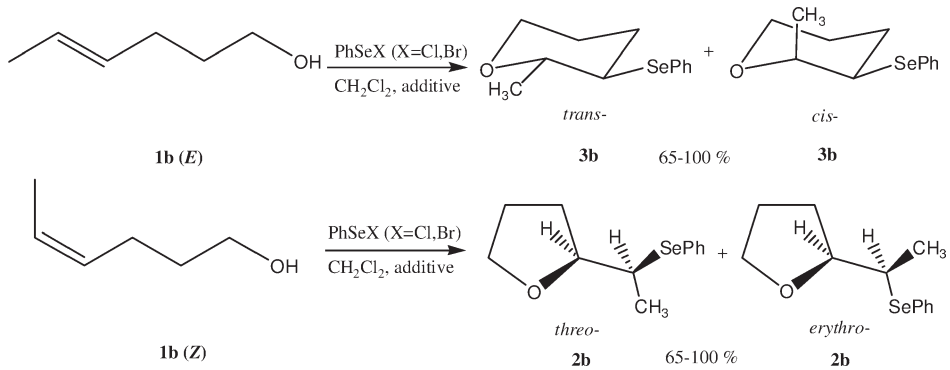


Table 2

Phenylselenoetherification of (*Z*)- and (*E*)-hex-4-en-ols at different temperature and in the presence of pyridine.

	Yield and ratio of cyclic products/%		
Reagent	−78°C	0°C	Room temperature
(*E*)-hex-4-en-1-ol			
PhSeCl	85 (87:13)	83 (75:25)	81 (69:31)
PhSeCl/Py	100 (95:5)	100 (74:26)	100 (24:76)
PhSeBr	77 (80:20)	–	65 (65:35)
PhSeBr/Py	100 (92:8)	100 (86:14)	100 (20:80)
(*Z*)-hex-4-en-1-ol			
PhSeCl	78 (98:2)	75 (85:15)	72 (70:30)
PhSeCl/Py	100 (23:77)	100 (5:95)	100 (0:100)
PhSeBr	83 (33:67)	–	75 (30:70)
PhSeBr/Py	100 (14:86)	100 (8:92)	100 (0:100)

Table 3

Phenylselenoetherification of (*Z*)- and (*E*)-hex-4-en-1-ols in the presence of Lewis acids ($ZnCl_2$, $FeCl_3$, and $AlCl_3$).

	Yield and ratio of cyclic products/%			
Substrate	No additives	$ZnCl_2$	$FeCl_3$	$AlCl_3$
PhSeCl				
(*E*)-1b	81 (69:31)	92 (98:2)	89 (76:24)	91 (72:18)
(*Z*)-1b	72 (70:30)	96 (97:3)	98 (86:14)	89 (93:7)
PhSeBr				
(*E*)-1b	65 (65:35)	95 (95:5)	96 (82:18)	99 (97:3)
(*Z*)-1b	75 (30:70)	98 (96:4)	99 (95:5)	95 (92:8)

using UV light for visualization. For column chromatography, E. Merck silica gel (60, particle size 0.063–0.200 mm) was used. Alkenols used as substrates are commercially available. Reagents (PhSeCl and PhSeBr) were used as supplied by Aldrich. Dichloromethane was distilled from calcium hydride.

General procedure. All reactions were carried out on a 1 mmol scale. To a magnetically stirred solution of 1 mmol of alkenol and 1 mmol of additive (0.162 g $FeCl_3$, 0.136 g $ZnCl_2$, or 0.134 g $AlCl_3$) in 5-mL dry dichloromethane was added 0.212 g solid PhSeCl (1.1 mmol) or 0.260 g PhSeBr (1.1 mmol) at room temperature until the solid dissolved. The reaction went to completion virtually instantaneously. Solution was washed with saturated $NaHCO_3$ aqueous solution and brine. Organic layer was dried over Na_2SO_4, concentrated, and chromatographed. The products were obtained after the elution of the traces of diphenyl diselenide on a silica gel–dichloromethane column. All the products were characterized and identified on the basis of their spectral data. Cyclic ether products were known compounds and their spectral data have been presented previously [18a].

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