Cyclization of Unsaturated Alcohols. Mild and Efficient Selenocyclization of Pent-4-en-1-ol

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An innovative route for intramolecular cyclization of pent-4-en-1-ol has been delineated through a ring closing reaction with phenylselenyl halides, in good yield. Several catalysts (triethylamine, quinoline, 2,2′-bipyridine, pyridine, $CoCl_2$ and $SnCl_2$) enable fast, facile and efficient cyclization.

Key words: Alcohol, Cyclization, Catalyst

Introduction

Electrophilic cyclizations of alkenyl carboxylic acids, alcohols, amines, amides, and functionalized dienes with participation of seleniranium ions have been broadly applied for the syntheses of diverse heterocyclic and carbocyclic compounds [1 – 6]. Applications of selenium reagents in organic chemistry have developed rapidly over the past years. Cyclic ether units (products of unsaturated alcohols and selenium reagents) are important synthetic targets in organic and medicinal chemistry due to their widespread occurrence in many complex natural compounds exhibiting important biological activities [7]. A number of synthetic approaches have been devised in order to construct the cyclic ether moiety [8]. In many respects selenocyclofunctionalization has the advantage that the introduction of the heteroatom, the manipulation of the obtained product and the removal of the function are facilitated by simple and mild reaction conditions [9].

For some time we have been involved in the development and exploration of new methods for cyclofunctionalization of unsaturated alcohols [10 – 13]. Rather new, however, is the use of some catalysts in selenocyclofunctionalization. An overview of the applications of some catalysts in the synthesis of cyclic phenylselenoethers is presented in this work. We used pent-4-en-1-ol as a simple representative of unsaturated alcohols.

Results and Discussion

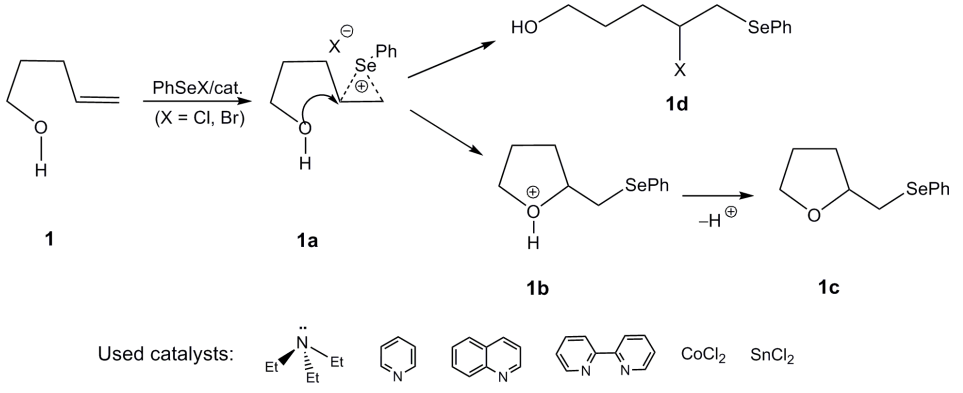
Phenylseleno-etherification of pent-4-en-1-ol can afford a tetrahydrofuran or a tetrahydropyran ring through 5-*exo*-trig or 6-*endo*-trig cyclization. Our previous research on this alkenol showed that only the five-membered ring system **1c** (Scheme 1) was obtained with a yield of 69 % in the case of PhSeCl as a reagent, and 63 % in the case of PhSeBr. Since there is no steric bulkiness in the alkenol system, the main reaction product is determined by the nucleophilic attack on the product with Markovnikov's orientation.

However, the presence of the nucleophilic halide anions is sometimes responsible for some undesirable processes such as the addition of the halide ion (**1d**, Scheme 1), which causes a lower yield of the cyclic ether product. In order to decrease the side reaction and to increase the yields of cyclic products we performed experiments with two different Lewis acidic ($SnCl_2$, $CoCl_2$,) and Lewis basic (triethylamine, pyridine, quinoline, 2,2′-bipyridine) sets of catalysts. Reactions were performed in the presence of catalytic and equimolar amounts of catalysts. The results of these investigations are given in Tables 1 and 2 showing that all reactions proceeded with excellent yields.

Table 1. Phenylselenocyclization of pent-4-en-1-ol in the presence of catalytic and equimolar amounts of Lewis acids.

Lewis acid	Equivalents of additive	Yields (%) with PhSeCl	Yields (%) with PhSeBr
$SnCl_2$	0.1	99	100
	1	97	96
$CoCl_2$	0.1	96	87
	1	100	88

In Table 1 the results of Lewis acid-promoted reactions are presented. The best results in terms of yields and minimization of side reactions were achieved with $SnCl_2$ as a catalyst, especially in the case of catalytic amounts of additive. The role of Lewis acids in these reactions is to increase the electrophilicity of the reagent (PhSeX) and to inhibit halide addition by removing the anion from the reagent and in that way to improve yields of the desired products.



Scheme 1. Mechanism of phenylselenoetherification of pent-4-en-1-ol.

Table 2. Phenylselenocyclization of pent-4-en-1-ol in the presence of equimolar and catalytic amounts of Lewis bases.

Lewis base	Equivalents of additive	Yields (%) with PhSeCl	PhSeBr
Triethylamine	0.1	100	100
	1	100	100
Pyridine	0.1	98	99
	1	99	100
Quinoline	0.1	98	99
	1	99	99
2,2′-Bipyridine	0.1	100	100
	1	98	100

From the data in Table 2 (with Lewis bases as catalysts) it can be seen that the cyclization process is the favored pathway. The best results were obtained when the reaction was performed in the presence of a catalytic and equimolar amounts of Et_3N, with both reagents (PhSeCl and PhSeBr). It appears that the presence of bases is beneficial to the cyclization process. Bases can enhance the nucleophilicity of the hydroxyl group of the alkenol by formation of a hydrogen bond. A base can also mediate the stabilization of the oxonium ion intermediate **1b** by abstracting a proton. It is possible that aromatic bases (pyridine, quinoline, 2,2′-bipyridine) are engaged in π-π interactions with the reagent (PhSeX) by arene-heteroarene ring stacking [14 – 17].

Experimental Section

Gas-liquid chromatography (GLC) analysis was performed with a Deni instrument, model 2000 with capillary apolar columns. ^1H and ^{13}C NMR spectra were run in $CDCl_3$ on a Varian Gemini 200 MHz NMR spectrometer. IR spectra were obtained with Perkin-Elmer Model 137B and Nicolet 7000 FT spectrophotometers. Microanalyses: Dornis und Kolbe, Mikroanalytisches Laboratorium, Mülheim a. d. Ruhr (Germany). Thin-layer chromatography (TLC) was carried out on 0.25 mm E. Merck precoated silica gel plates (60F-254) using UV light for visualization. For column chromatography, E. Merck silica gel (60, particle size 0.063 – 0.200 mm) was used.

All reactions were carried out on a 1 mmol scale. To a magnetically stirred solution of alkenol (1 mmol) and catalyst (0.1 mmol or 1 mmol) in dry dichloromethane (5 ml) solid PhSeCl (0.212 g, 1.1 mmol) or PhSeBr (0.260 g, 1.1 mmol) was added at r. t. The reaction went to completion in a few minutes. The pale-yellow solution was washed with 1 M HCl (only in case of basic additives), followed by saturated aqueous $NaHCO_3$ solution and water. The organic layer was dried over Na_2SO_4, concentrated and chromatographed. The product was obtained after the eluation of the traces of diphenyl diselenide from a silica gel-dichloromethane column. The product was characterized and identified on the basis of its spectral data [13].

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