Monatsh Chem 139, 1373–1376 (2008)
DOI 10.1007/s00706-008-0936-y
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Rapid $SnCl_2$ catalyzed phenylselenoetherification of (*Z*)- and (*E*)-hex-4-en-1-ols

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Received 13 March 2008; Accepted 18 March 2008; Published online 2 June 2008

Abstract A fast and efficient method for intramolecular heterocyclization of (*Z*)- and (*E*)-hex-4-en-1-ols was developed. The method does not cause side reactions of the substrates and provides the cyclic phenylselenoethers in high yields after only few minutes. A catalytic amount of $SnCl_2$ increased the yield, but in the presence of an equimolar amount of $SnCl_2$, formation of corresponding cyclic ethers were almost quantitative and reaction occurred instantaneously under extremely mild experimental conditions.

Keywords Alcohol; Cyclization; Phenylselenoetherification; $SnCl_2$.

Introduction

Practical syntheses of cyclic ethers have attracted considerable attention in organic, pharmaceutical, or medical chemistry, since this basic skeleton occurs broadly in natural products and biologically active substances. Cyclofunctionalization of unsaturated alcohols is a very popular reaction providing easy access to cyclic ethers [1–6]. These cyclizations are well documented in literature as convenient pathways in the synthesis of natural products and related compounds [7]. During the last years, cyclic ether synthesis has become of common use because a cyclization reaction can directly build complicated molecules from readily accessible starting materials under mild conditions. Cyclic ethers are present in the skeletons of several groups of natural compounds exhibiting important biological activities [8]. These units can be found in monocyclic or polycyclic compounds, fused with other cyclic ethers or forming spiro systems [9]. The presence of molecules with oxygenated heterocycles in nature is receiving considerable attention considering their capacity of modification of the transport of the Na^+, K^+, and Ca^{2+} cations through lipid membranes [10–13]. This activity is responsible for their antibiotic [10], neurotoxic [14, 15], antiviral [16], and cytotoxic action [17, 18] and as growth regulators [10, 19, 20] or inhibitors of the level of cholesterol in blood [21].

In many respects selenocyclofunctionalization of unsaturated alcohols 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 condition required [5, 6, 22]. This methodology has been extended to more complex systems having alcohol and double bond functions.

For some time we have been involved in the development and exploration of new methods for cyclofuncionalization of substituted unsaturated alcohols [23–26]. We have investigated the regioselectivity of this cyclofunctionalization reaction by means of *Ph*SeCl and *Ph*SeBr as a function of alkyl substitution at the unsaturated carbon atoms and at

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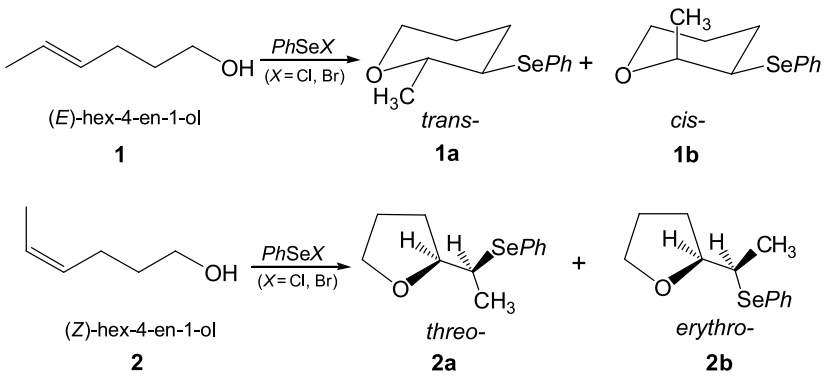
the carbinol carbon atom [23]. In the past few years attention has been focused on the synthesis of the substituted tetrahydropyranes and tetrahydrofuranes as key starting materials for the preparation of numerous heterocyclic compounds including physiologically active products. Substituents at the olefinic double bond decreases the yield of the cyclic ether products, but substituents at the carbinol carbon atom show a stronger influence on the decreasing of the yields. Thus, secondary alkenols cyclize to a considerably lower extent, while tertiary alkenols are not converted into cyclic products at all by *Ph*SeBr and in a small extent with *Ph*SeCl. The steric influence of substituents is clearly demonstrated in that case. Hence, of particular importance is discovering of the appropriate experimental conditions under which phenylselenocyclization of tertiary alkenols would readily be accomplished in synthetically useful yields, regardless of the reagent used. Thus we found that in the presence of pyridine tertiary alkenols cyclized in quantitative yields [24]. We explored this method on the primary and secondary alcohols and found the same effect [27].

Next, we turned our attention to the other catalyst. The present study considers the phenylselenocyclization of (*Z*)- and (*E*)-hex-4-en-1-ols in the presence of $SnCl_2$.

Results and discussion

In connection to expanding the generality of catalytic ring-closing reactions, (*Z*)- and (*E*)-hex-4-en-1-ols (**1** and **2**, Schemes 1 and 2) in the presence of $SnCl_2$ were subjected to phenylselenyl halides (*Ph*Se*X*, $X = Cl$, Br). In the presence of a catalytic amount of $SnCl_2$ yields of cyclic ethers products increase rapidly. When the reactions were carried out in the presence of equimolar amount of $SnCl_2$ an instantaneous cyclization occurred and almost quantitative yields of cyclic ether products were obtained (Scheme 1 and Table 1). This seems to be due to the participation of $SnCl_2$, which can stabilize the episelenonium ion intermediate (**1c** and **2c**, Scheme 2), but the details are not yet clear.

We describe herein the details of this new procedure. The procedure employs phenylselenyl chloride and bromide, and a catalytic or equimolar amount of $SnCl_2$ to generate an episelenonium ion intermediate (**1c**, **2c**, Scheme 2) from which the cyclic ether product tetrahydropyran (**1a**, **1b**) or tetrahydrofuran (**2a**,

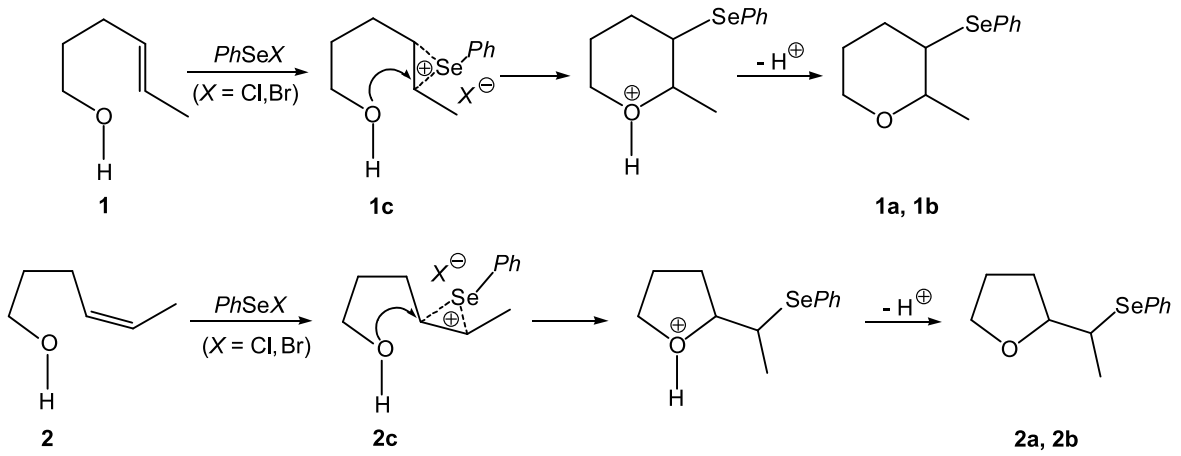


Scheme 1

Table 1 $SnCl_2$ catalyzed phenylselenoetherification of (*Z*)- and (*E*)-hex-4-en-1-ols

Substrates	Products	Yields and ratio (**a**:**b**) of cyclic products/%					
		*Ph*SeCl			*Ph*SeBr		
		A	B	C	A	B	C
1	**1a**, **1b**	81 (69:31)	98 (96:4)	96 (97:3)	65 (65:35)	99 (96:4)	100 (97:3)
2	**2a**, **2b**	72 (70:30)	99 (87:13)	100 (97:3)	75 (30:70)	98 (82:18)	99 (84:16)

A – without addtitive; B – with catalytic amount of $SnCl_2$; C – with equimolar amount of $SnCl_2$



Scheme 2

2b) type arise by internal nucleophilic displacement. The results of our investigation are shown in Table 1 and in the Schemes 1 and 2.

As it can be seen from the results obtained the presence of $SnCl_2$ plays an important role in chemoselection of the reaction and in regio- and stereoselection of the produced oxacyclic compounds. Therefore, the reaction seems to proceed as follows: *Ph*Se*X* approaches the double bond moiety of the alkenols (**1** and **2**, Scheme 2). Intramolecular capture of the selenonium species (**1c** and **2c**) by an internal hydroxyl nucleophile, which is facilitated by the presence of $SnCl_2$, results in the formation of a rings **1a** and **1b** or **2a** and **2b** depending on the structure of starting alkenol.

Δ^4-Alkenol (hex-4-en-1-ol) **1** with (*E*)-configuration in contrast to **2** ((*Z*)-configuration) affords six-membered cyclic ethers **1a** and **1b** as unique products (Table 1, Scheme 1). (*Z*)-Hex-4-en-1-ol (**2**) affords only five-membered cyclic ethers **2a** and **2b**. The ratio of *trans-*/*cis*-tetrahydropyranyl ethers **1a** and **1b** depends on experimental conditions. In all reactions the *trans* product predominates, especially in the case of an equimolar amount of $SnCl_2$.

Tetrahydrofuranyl ethers **2a** and **2b** are the only products in the reactions with (*Z*)-hex-4-1-ol. Ratio of *threo*- (**2a**) and *erythro*- (**2b**) isomers in the reaction without additive depends of the reagent used. In the reaction with *Ph*SeCl *erythro*-isomer predominates (70:30) but with *Ph*SeBr *threo*-isomer is the main product. Presence of $SnCl_2$ changes the distribution of *threo-*/*erythro*-isomers. In all cases *threo*-isomer generates in higher yields. This is due to the presence of $SnCl_2$.

The possible role of $SnCl_2$ as an additive is to remove halide ions from reagent (*Ph*SeCl and *Ph*SeBr). In this way the electrophilicity of the reagent is increased and the halide ions are removed from reaction, so the side products of halide attack as a nucleophile on an episelenonium ion (which results as addition reaction on the double bond) are minimal.

Experimental

GM analysis were obtained with a Agilent Technologies instrument, model 6890 N with HP-5NS columns (5% phenyl 95% methylpolysyloxane). ^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 Model 137B and Nicolet 7000 FT spectrophotometers. Microanalyses were performed by "Dornis and Colbe" and found to be in good agreement with the calculated values. 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. Olefinic alcohols used as substrates are commercially available. Reagents (*Ph*SeCl and *Ph*SeBr) 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 0.1 g alkenol (1 mmol) and 0.019 g or 0.19 g $SnCl_2$ (0,1 mmol or 1 mmol) in 5 cm^3 dry dichlomethane was added 0.212 g solid *Ph*SeCl (1.1 mmol) or 0.260 g *Ph*SeBr (1.1 mmol) at room temperature until the solid dissolved. The reaction went to completion virtually instantaneously. Pale yellow solution was washed with saturated $NaHCO_3$ aqueous solution and brine. Organic layer was dried (Na_2SO_4), concentrated, and chromatographed. TLC and GM analysis as well as NMR spectra showed complete conversion of starting alkenol to cyclic ether product. The product was

obtained after the eluation 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 [23].

Acknowledgement

This work was funded by the Ministry of Science, Technology and Development of the Republic of Serbia (Grant: 142008).

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