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Pyridine-Facilitated Phenylselenoetherification of Some Tertiary Alkenols

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ABSTRACT: *An improved procedure for intramolecular cyclization of tertiary alkenols using benzeneselenyl halides has been developed. We found that cyclization can be facilitated by pyridine. Thus, in the presence of an equimolar amount of pyridine, a chemospecific reaction could be observed that resulted in formation of corresponding cyclic ethers, and quantitative yields were achieved instantaneously under extremely mild experimental conditions. The effect of the halide ion of the selenylating reagent is not significant, both halides generally giving equal results.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:475–479, 2001

INTRODUCTION

Unsaturated substrates carrying internal nucleophiles (COOH, OH, SH, SAc, NHCOOEt, CH_2 $SnMe_3$, etc.) were found to react smoothly with certain organoselenium reagents to afford cyclic systems [1–4]. Among the various types of cyclic systems to be synthesized according to this general methodology are lactones [3], ethers [5], thioethers [6], nitrogen heterocycles [7], and carbocycles [8]. The syntheses of these classes of compounds play an important role in the construction of biologically active prostacyclines [9] and other naturally occurring products [10].

Intramolecular cyclization of unsaturated alcohols to cyclic phenylselenoethers (termed phenyselenoetherification) by means of organoselenium reagents has become an important tool for the synthesis of oxacyclic compounds [11]. In continuation of our studies on the electrophile-assisted intramolecular cyclization of alkenols [12–14], we have investigated the regioselectivity of this cyclofunctionalization reaction by means of PhSeCl and PhSeBr as a function of alkyl substitution at the unsaturated carbon atoms and at the carbinol carbon atom [15]. Intramolecular heterocyclization is the main reaction in the case of all investigated primary and secondary Δ^4- and Δ^5-alkenols, PhSeCl has been more efficient than PhSeBr in terms of yield and regioselectivity. Also, the influence of the reaction temperature and structure of the substrate is more significant in the reaction with PhSeBr. 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 PhSeBr and to a small extent with PhSeCl. The steric influence of substituents is clearly demonstrated in that case. Substituted tetrahydrofuran and tetrahydropyran rings are common in many natural products and thus play an important role as building blocks for the synthesis of various biologically active organic target molecules [16,17]. Hence, of particular importance is the discovery of the appropriate experimental conditions under which phenylselenocyclization of tertiary alkenols would readily be

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accomplished in synthetically useful yields, regardless of the reagent used.

RESULTS

In order to have synthetic utility, we studied the intramolecular cyclization of some tertiary alkenols by means of benzeneselenyl halides (PhSeX, X=Cl, Br) under a variety of conditions, including the altering of reaction temperature (from −78°C to room temperature), solvents, reaction time, and concentration of the reactants, but all the attempts to improve yield of the cyclized products were unsuccessful. However, it turned out that cyclization could be facilitated by pyridine. In the presence of pyridine, a chemospecific reaction was observed that resulted in formation of corresponding cyclic ethers, and quantitative yields were achieved instantaneously under extremely mild experimental conditions. We describe herein the details of this new procedure.

We were interested in exploring how PhSeX behaves in the presence of some additives and have therefore undertaken a study of the reaction of tertiary alkenols with PhSeX in the presence of base. As it seemed essential to remove HX, the reactions were performed in the presence of $NaHCO_3$ and triethylamine, but there was not any significant effect on the yield. Finally, when the reactions were carried out in the presence of an equimolar amount of pyridine, an instantaneous cyclization occurred, and quantitative yields of cyclic ether products were obtained.

Here we report on the results of pyridine-facilitated phenylselenoetherification of some tertiary Δ^4- and Δ^5-alkenols by PhSeX (X=Cl, Br) to afford the corresponding cyclic ethers. The results of our investigation are shown in Tables 1 and 2 and in Figures 1–4. By the reaction of 2,6-dimethyl-hept-6-en-2-ol (**5**), 2,6-dimethyl-hept-5-en-2-ol (**7a**), linalool (**7b**), nerolidol (**7c**), and α-terpineol (**10**) with benzeneselenyl halide, cyclization by the oxygen atom proceeded to form oxygen heterocycles bearing the phenylseleno moiety (**3** and/or **4**) (Figure 1). As it can be seen from the results obtained, the presence of pyridine play an important role in chemoselection of the reaction and in regioselection and stereoselection of the produced oxacyclic compounds.

DISCUSSION

Cyclization of the simplest alkenol in this series, 2,6-dimethyl-hept-6-en-2-ol (**5**), with PhSeX occurs instantaneously producing essentially a sole tetrahydropyran product (**6**) in quantitative yield (Figure 2). It is in accordance with the ionic mechanism of this reaction and may be ascribed to the thermodynamic stability of the cyclized product.

In the case of alkenols with a terminally disubstituted double bond (**7**), although the Markovnikov rule requires that the PhSe group be added at the less substituted carbon to afford the more stable carbenium ion, the reaction is mostly dominated by stereoelectronic effects that favor attack of the oxygen at the less substituted carbon, producing as the major products tetrahydrofuran derivatives (**8**) (Figure 3). This fact might play an important role in the preparation of tetrahydrofurans because of the widespread occurrence among natural products of structures with a five-membered ring-incorporated oxygen.

2,6-Dimethyl-hept-5-en-2-ol (**7a**) cyclizes quantitatively, affording five- and six-membered cyclic ethers in a ratio of 88:12 at room temperature. Regioselectivity could be improved by performing the reaction at the lower temperature. In comparison with previous results [15], the regioselectivity at −78°C is the same, but at room temperature is much better (Table 1).

Table 1 reveals that quantitative yields and high regioselectivity are achieved even at room temperature.

Linalool (**7b**) cyclizes in the same way, and similar regioselectivity is obtained. It seems that pyridine plays an important role in stereoselection of the

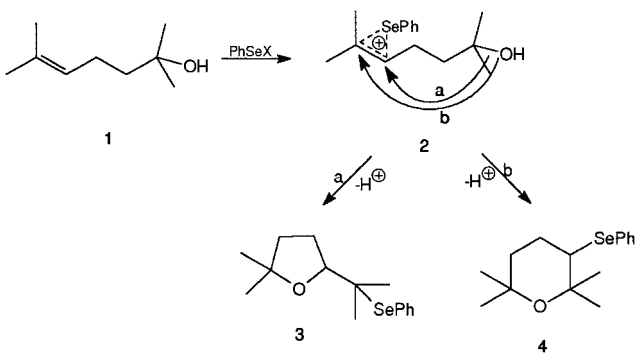


FIGURE 1

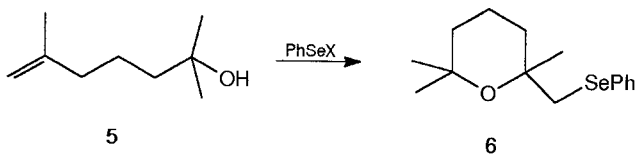
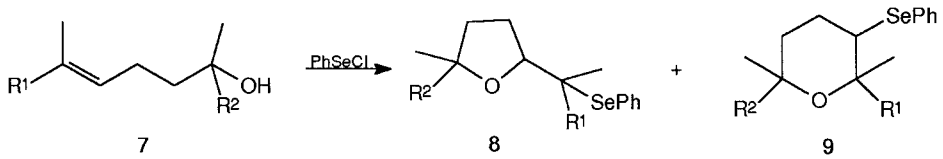


FIGURE 2



7a) $R^1 = CH_3$; $R^2 = CH_3$; **8a** (88 :12) **9a**
7b) $R^1 = CH_3$; $R^2 = CH{=}CH_2$; **8b** (86 :14) **9b**
7c) $R^1 = CH_2CH{=}C(CH_3)_2$; $R^2 = CH{=}CH_2$; **8c** (92 : 8) **9c**

FIGURE 3

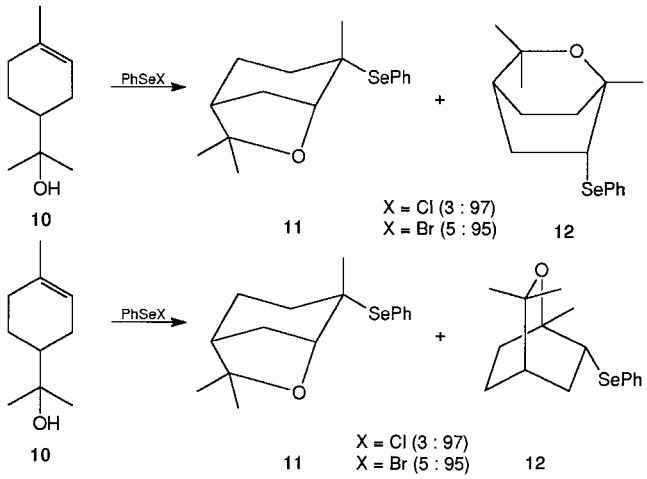


FIGURE 4

produced cyclic ethers. The major product in this reaction, a tetrahydrofuran derivative (**8b**), is formed in a trans:cis ratio of 34:66. In such a reaction, the stereochemistry of the product is the opposite of that obtained previously [15] (trans:cis ratio 70:30). The high cis selectivity among the stereomers of (**8b**) may be due to the participation of pyridine. Pyridine allows the reaction to be carried out under kinetic conditions, probably explaining the reversal of stereoselectivity.

Nerolidol **(7c)** behaves like linalool in the reaction with PhSeX, affording predominantly tetrahydrofuran derivative **(8c)** in a trans:cis ratio of 32:68. As indicated in Table 2, in this case, regioselectivity is the highest regarding to the effects of steric hindrance.

In the case of a constitutionally similar case to the aforementioned alkenols **(7)**, but with cyclic, α-terpineol **(10)**, the same behavior was expected. By contrast, the tetrahydropyran derivative predominates presumably because of electronic and conformational factors. In this case, the release of much strain energy may be accomplished by forming the product **12** rather than the originally expected **11** (Figure 4).

In conclusion, the aforementioned results clearly indicate that there is no difference in reactivity between PhSeCl and PhSeBr (Table 2). As far as we know, it is the first example where these two

TABLE 1 Phenylselenoetherification of 2,6-Dimethyl-hept-5-en-2-ol

	Yield (%) (Ratio of Products **8a** *and* **9a***)*		
Reagent	*−78°C*	*0°C*	*Room Temperature*
PhSeCl	75 (95:5)	43 (66:34)	37 (55:45)
PhSeCl/Py	100 (95:5)	100 (87:13)	100 (88:12)

TABLE 2 Phenylselenoetherification of Some Tertiary Alkenols at Room Temperature

		Yields of Cyclic Ether Products (%)			
Substrate	*Products*	*PhSeCl*[a]	*PhSeBr*[a]	*PhSeCl/py*[b]	*PhSeBr/py*[b]
5	**6**	31	n.c.p.[c]	100	100
7a	**8a + 9a**	37	n.c.p.[c]	100 (88:12)[d]	100 (87:13)[d]
7b	**8b + 9b**	46	n.c.p.[c]	100 (86:14)[d]	100 (84:16)[d]
5	**6**	23	n.c.p.[c]	100 (92:8)[d]	100 (90:10)[d]
7a	**8a + 9a**	34	n.c.p.[c]	100 (3:97)[d]	100 (1.5:98.5)[d]

[a]Isolated yields.
[b]These are absolute yields determined by GLC relative to an internal standard. Isolated yields did not differ significantly from chromatographically determined yields.
[c]n.c.p., no cyclized product. Diphenyl diselenide was recovered almost quantitatively, but unreacted starting alkenol was not recovered. Products were polar and could not be analyzed by TLC. In another experiment we monitored the reactions of these alkenols with PhSeBr by ^{1}H NMR spectroscopy. The signals corresponding to starting alkenol disappeared and new signals appeared assignable to the corresponding bromide of the alcohol. However, the attempted isolation of these products resulted in the isolation of only diphenyl diselenide due to the polimerization of the bromides on the column.
[d]Relative distribution of the THF- and THP-type phenylseleno ether products (given in parentheses) was evaluated by capillary GLC and ^{1}H NMR analysis.

reagents have the same behavior. PhSeBr is known to be a superior reagent only for effecting intramolecular amidoseleniations of *N*-alkenylamides [18]. Previous results obtained in the reactions of alkenols with PhSeX indicate that PhSeCl is a more efficient reagent for cyclization than PhSeBr [15]. This observation may be ascribed to the role of the pyridine. It appears that the presence of pyridine is beneficial to the cyclization process and more likely due to its basic properties. In addition, pyridine could enhance the nucleophilicity of the hydroxyl group of the alkenol and also mediate the stabilization of the oxonium ion intermediates by abstracting the proton. It seems that pyridine could play several roles. On the whole, its presence serves to increase the efficiency of the cyclization process. This reaction not only has enormous potential for the regioselective synthesis of substituted tetrahydrofuran and tetrahydropyran derivatives, but also opens a new area involving the use of pyridine as an additive in cyclization reactions.

This improved procedure for phenylselenoetherification should often prove the simplest and superior to those currently available. As for the yields of cyclic ethers, the procedure described in this article gave better results than reported procedures. Accompanied by other merits, such as the mildness of the reaction conditions and the simplicity of the experimental procedure, our procedure is the most attractive one for the conversion of alkenols into oxacyclic compounds. Moreover, we are confident pyridine-facilitated seleniation will be of general use for a facile synthesis of various heterocycles.

EXPERIMENTAL

General Methods

Gas–liquid chromatography (GLC) analysis was performed with a Deni instrument, model 2000 with capillary apolar columns. ^{1}H 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 were performed by Dornis and Colbe. 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.

Materials

All the olefinic alcohols used as substrates are known compounds, some of which **(7b, 7c,** and **10)** are commercially available, while the other ones **(5** and **7a)** were synthesized from 2,6-dimethyl-hept-5-en-2-one and 2,6-dimethyl-hept-6-en-2-one respectively (commercially available), according to the known procedure. Reagents (PhSeCl and PhSeBr) were used as supplied by Aldrich. Methylene chloride was distilled from calcium hydride.

General Procedure

All reactions were carried out on a 1 mmol scale. To a magnetically stirred solution of alkenol (1 mmol) and pyridine (0.087 g, 1.1 mmol) in dry methylene chloride (5 mL) was added solid PhSeCl (0.212 g, 1.1 mmol) or PhSeBr (0.260 g, 1.1 mmol) at room temperature until the solid dissolved. The reaction went to completion virtually instantaneously. PhSeCl and PhSeBr worked equally well. The pale yellow solution was washed with 1 M HCl aqueous solution (5 mL), saturated $NaHCO_3$ aqueous solution, and then brine. The organic layer was dried over $Na_2\ SO_4$ and concentrated, and chromatography was performed. The TLC and GLC analyses and NMR spectra showed complete conversion of the starting alkenol to the cyclic ether product. The product was obtained after the elution of the traces of diphenyl diselenide from a silica gel-methylene chloride column. All the products were characterized and identified on the basis of their spectral data. The cyclic ether products were known compounds, and their spectral data had been given previously [15,19].

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