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An Efficient Route to Phenylselenoethers in the Presence of Ag_2O

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Summary. An efficient protocol for the preparation of phenylselenoethers from unsaturated alcohols using phenylselenenyl halides at room temperature was developed. The procedure employs phenylselenenyl chloride and bromide, some Δ^4- and Δ^5-alkenols and Ag_2O, as an additive, to generate the tetrahydropyrans or tetrahydrofurans. This method permits the preparation of cyclic phenylselenoethers in high yields and under extremely mild conditions.

Keywords. Additive; Alcohol; Cyclization; Phenylselenoetherification.

Introduction

Substituted tetrahydrofuran and tetrahydropyran ring systems are common structural units found in many bioactive natural products. Consequently, the development of strategies for the stereocontrolled synthesis of substituted tetrahydrofurans and tetrahydropyrans is an area of considerable ongoing interest [1, 2]. The presence in Nature of molecules with oxygenated heterocycles is receiving significant attention considering their capability to transport the metallic cations Na^+, K^+, and Ca^{2+} through lipid membranes [3–6]. This activity is responsible for their antibiotic [3], neurotoxic [7, 8], antiviral [9], and cytotoxic action [10, 11] and as growth regulators [3, 12, 13] or inhibitors of the level of cholesterol in blood [14], *etc*.

A number of synthesis approaches have been devised in order to construct the cyclic ether moiety using either a carbon–carbon or a carbon–oxygen cyclization step or modifying cyclic precursor. Among them, cyclofunctionalization of unsaturated alcohols is a very popular reaction providing easy access to cyclic ethers. 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 condition [15–23]. This methodology has also been extended to more complex systems having alcohol and double bond functions.

In 1973 the biochemical role of selenium in mammals has been established. It has been found that it is part of the active site of the antioxidant enzyme glutation peroxidase [24, 25]. During the next decade came the explosive growth in the use of organoselenium compounds. Very soon it has been found that the phenylselenenyl groups are very good electrophilic reagents in organic synthesis, and in reactions with olefinic bonds they very often produce regio- and stereoselective products.

Results and Discussion

In recent years, we have been interested in the synthesis of oxygenated heterocyclic rings *via* intramolecular cyclization of alkenols by means of phenylselenenyl halides [18], *Ph*Se*X* (*X* = Cl, Br). We have reported that 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 *Ph*SeBr and in

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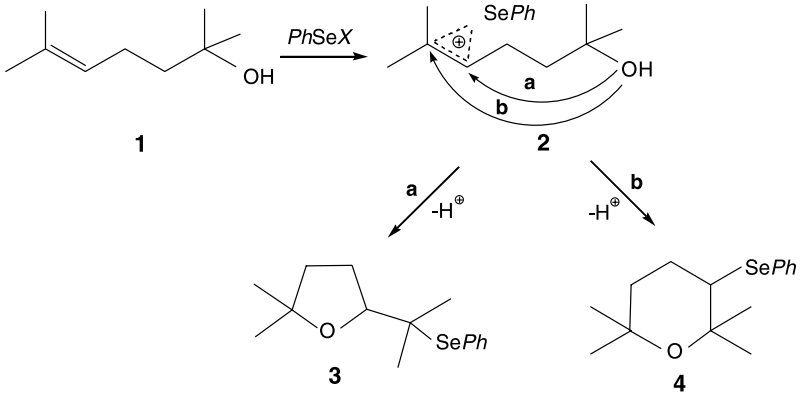
only a small amount with *Ph*SeCl. Recently, we have found an approach to cyclic ethers from tertiary alkenols using *Ph*Se*X* ($X = Cl$, Br) in the presence of pyridine [19, 22]. We found that pyridine as additive enables fast and facile cyclization and very high yields of cyclic ethers were obtained.

The present paper describes an easy access to cyclic ethers, *THP* or *THF* type, bearing a phenylseleno moiety in which the yields exceed 70% (in some cases 90%) and with a little or no purification required. The procedure works smoothly resulting in almost quantitative formation of the cyclic ethers in the presence of Ag_2O as the catalyst. The results of our investigation are displayed in Tables 1 and 2 and in Schemes 1, 2, and 3. The results obtained show that all reactions proceeded to form oxygen heterocycles bearing the phenylseleno moiety in high yields. The cyclization using a stoichometric amount of Ag_2O was completed faster than those using a catalytic amount. On the other hand, the reaction without a catalyst in some cases (**8b**–**8e**) did not afford the desired product in practical yield

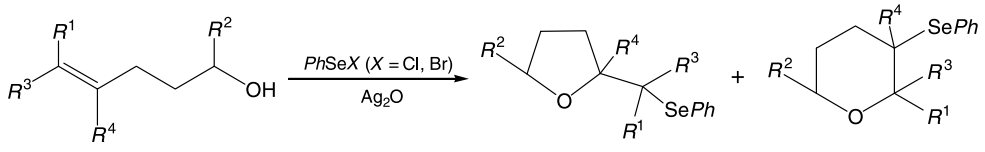
Table 1. Phenylselenoetherification of some Δ^4-alkenols in the presence of a catalytic and equimolar amount of Ag_2O, A···*Ph*SeCl, B···*Ph*SeBr

Substrate	Products	Yields of cyclic ether products/%[a]					
		A	A/Ag_2O cat.	A/Ag_2O eq.	B	B/Ag_2O cat.	B/Ag_2O eq.
5a	**6a**	69	97	99	63	86	94
5b	**6b**	92	99	100	64	88	95
5c	**6c**	86	90	95	47	65	90
5d	**6d**	72	93	97	75	90	92
5e	**7e**	81	95	99	65	88	95

[a] Isolated yields of Δ^4-alkenols [18]



Scheme 1



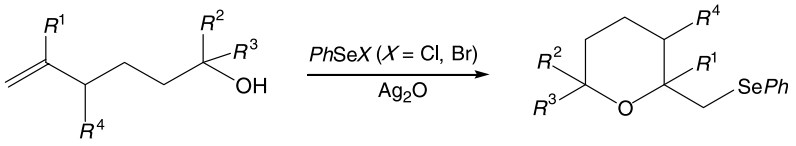
5a $R^1 = R^2 = R^3 = R^4 = H$ — **6a**
5b $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$ — **6b**
5c $R^1 = R^3 = R^4 = H$, $R^2 = CH_3$ — **6c**
5d $R^2 = R^3 = R^4 = H$, $R^1 = CH_3$ (*Z*) — **6d**
5e $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$ (*E*) — **7e**

Scheme 2

Table 2. Phenylselenoetherification of some Δ^5-alkenols in the presence of a catalytic and equimolar amount of Ag_2O, A···*Ph*SeCl, B···*Ph*SeBr

Substrate	Products	Yields of cyclic ether products/%[a]					
		A	A/Ag_2O cat.	A/Ag_2O eq.	B	B/Ag_2O cat.	B/Ag_2O eq.
8a	**9a**	81	98	100	75	86	98
8b	**9b**	80	90	100	26	78	97
8c	**9c**	31	69	96	0	55	87
8d	**9d**	33	71	97	0	59	88
8e	**9e**	30	68	87	0	54	81

[a] Isolated yields of Δ^5-alkenols [18]



8a $R^1 = R^2 = R^3 = R^4 = H$ — **9a**
8b $R^1 = R^2 = CH_3, R^3 = R^4 = H$ — **9b**
8c $R^1 = R^2 = R^3 = CH_3, R^4 = H$ — **9c**
8d $R^1 = H$, $R^2 = CH(CH_3)_2, R^3 = R^4 = CH_3$ — **9d**
8e $R^1 = R^3 = H, R^2 = CH_3C{=}CH_2, R^4 = CH_3$ — **9e**

Scheme 3

(**9b**–**9e**). Cyclization is facilitated by the presence of Ag_2O. Also, the additive caused a dramatic increase in the reaction rate. All reactions were finished within a few minutes (without additives reaction time is half an hour to several hours). As we can see from the results in Tables 1 and 2, primary (**5a**, **5b**) and secondary (**5c**) Δ^4-alkenols with a terminal double bond as well as Δ^4-alkenols with a terminally monosubstituted double bond (**5d**) afford regioselectively the five-membered cyclic ethers (**6a**, **6b**, **6c**, and **6d**). The Δ^4-alkenol **5e** with (*E*)-configuration in contrast to **5d** ((*Z*)-configuration) affords the six-membered cyclic ether **7e** as a unique product (Table 1, Scheme 2). The yields of cyclic ethers are higher by about 20% in comparision with yields without additive.

To extend the generality of this reaction, cyclization of various primary, secondary, and tertiary Δ^5-alkenols was carried out under optimized conditions, the results are displayed in Table 2 and in Scheme 3. These alkenols gave tetrahydropyrans, which are commonly encountered substructures in many natural products showing interesting biological properties, the most prominent of these being polyether antibiotics such as monensin, narasin, and tetronomycin [3]. Hence, of particular importance is the discovery of the appropriate experimental conditions under which phenylselenocyclization of Δ^5-alkenols would readily be accomplished in synthetically useful yields, regardless of the reagent used. Cyclization of these alkenols was complete in a short time, producing the corresponding derivatives **9a**–**9e** in good to excellent yields.

All reactions proceeded to form six-membered oxygen heterocycles bearing the phenylseleno moiety. It is in accordance with the ionic mechanism of this reaction (Scheme 1) and may be ascribed to the thermodynamic stability of the cyclized product. Cyclization is facilitated by the presence of Ag_2O. Yields of products are higher and reaction time is shorter. Catalytic amounts of the additives cause higher yields, but an equimolar amount gives almost quantitative yields. Alkenols **8a** and **8b** reacted very fast and in very high yields (in the case of *Ph*SeCl and equimolar amount of additive yields are quantitative) but in the case of alkenols with larger substituents as in **8c**, **8d**, and **8e**, the yields decreased due to steric hindrance. Depending on the mechanism, this can indeed be expected. Obtained results are clear evidence that the presence of Ag_2O increase the yield of the cyclic ether products. The results are strongly supported by

the fact that the additive can bind the counter ion from the reagent (X^- from *Ph*Se*X*), increase electrophilicity of the *Ph*Se group facilitating the subseqent nucleophilic attack of the oxygen to form the desired ether, and eliminates X^- as a concurrent of the hydroxyl group in the cyclization step.

In conclusion, it appears that the above described conditions for the cyclization of Δ^4- and Δ^5-alkenols to five-membered and six-membered ethers are more advantageous in terms of time and yield than those previously reported for the same reagents. In addition, other conditions will be tested to increase the yields for the less effective alkenols. In view of the above we considered this improved procedure for preparing cyclic ethers and related systems as 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 that this procedure will be of general use for a facile synthesis of various heterocycles.

Experimental

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 with $CDCl_3$ as the solvent on a Varian Gemini 200 MHz NMR spectrometer. IR spectra were obtained with Perkin-Elmer Model 137B and Nicolet 7000 FT spectrophotometers. *Dornis* and *Colbe* performed the microanalyses, which agreed favourably 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.

General Procedure

All reactions were carried out on a 1 mmol scale. To a magnetically stirred solution of 1 mmol alkenol and 0.1 mmol or 1 mmol catalyst in 5 cm^3 dry CH_2Cl_2 0.212 g solid *Ph*SeCl (1.1 mmol) or 0.260 g *Ph*SeBr (1.1 mmol) were added at room temperature. The reaction went to completion within a few minutes. The pale yellow solution was washed with saturated $NaHCO_3$ and H_2O. The organic layer was dried over Na_2SO_4, concentrated, and chromatographed. The product was obtained after the eluation of traces of diphenyl diselenide from a silica gel-CH_2Cl_2 column. All products were characterized and identified on the basis of their spectral data [18].

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