Monatshefte für Chemie 134, 1359–1363 (2003)
DOI 10.1007/s00706-002-0596-2

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Phenylselenoetherification of Some Δ^5-Alkenols in the Presence of Pyridine, Ag_2O, and AgO*Ac* as Additives

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Received October 21, 2002; accepted (revised) November 13, 2002
Published online August 28, 2003

Summary. An improved procedure for intramolecular cyclization of some Δ^5-alkenols using *Ph*Se*X* (*X* = Cl, Br) was developed. We found that cyclization can be facilitated in the presence of pyridine, Ag_2O, and AgO*Ac* as additives. Thus, a catalytic amount of additive influenced higher yields and equimolar amounts achieved almost quantitative yields under extremely mild experimental conditions. The effect of the halide ion of the selenylating reagent was not significant.

Keywords: Additives; Alkenols; Cyclization; Heterocycles; Phenylselenyl halides.

Introduction

During the last years, cyclic ethers have attracted considerable attention due to their occurrence in several groups of natural compounds exhibiting important biological activities [1]. These units can be found in monocyclic or polycyclic compounds, fused with other cyclic ethers or forming spiro systems [2]. The presence of molecules with oxygenated heterocycles in nature is receiving considerable attention thinking of their capacity of transport modification of Na^+, K^+, and Ca^{2+} cations 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 cholesterol level in blood [14].

A number of synthetic approaches have been devised in order to construct the cyclic ether moiety, using a carbon–carbon [15–22] or a carbon–oxygen [23–34] cyclization step, or modifying a cyclic precursor [35–41].

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Results and Discussion

In recent years we have studied the intramolecular cyclizations of some Δ^4- and Δ^5-alkenols by means of benzeneselenenyl halides *Ph*Se*X* (*X* = Cl, Br) [29, 40–42]. Intramolecular heterocyclization is the main reaction in the case of all investigated primary and secondary alkenols, whereas tertiary alkenols, under the same experimental conditions are not converted into cyclic products at all by *Ph*SeBr, however, in low yields with *Ph*SeCl. Although additional products are expected, we have found that all investigated tertiary alkenols in the reaction with *Ph*SeBr [41] afforded γ- and δ-bromoalkanols in high yields (about 90%).

Recently [42], we have presented an approach to cyclic ethers from tertiary alkenols using *Ph*Se*X* (*X* = Cl, Br) in the presence of pyridine. We found that the yields of the cyclic ethers are quantitative. In this paper, we present the extension of the methodology to primary and secondary Δ^5-alkenols and with Ag_2O and AgO*Ac* as additives. These alkenols have given 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 can readily be accomplished in synthetically useful yields, regardless of the reagent used. The results of our investigation are shown in Tables 1 and 2 and in Scheme 1.

All reactions proceeded to form six-membered oxygen heterocycles bearing the phenylseleno moiety. This is in accordance with the ionic mechanism of this reaction and may be ascribed to the thermodynamic stability of the cyclized product. Cyclization is facilitated by the presence of pyridine, Ag_2O, and AgO*Ac*. Thus, yields of products are higher and reaction times are shorter. Catalytic amounts of additives influence higher yields, but an equimolar amount gives almost quantitative yields. As we can see from Tables 1 and 2, pyridine shows the best results if an equimolar amount is used and Ag_2O is the best catalyst for this type of cyclization. It appears that the presence of pyridine is beneficial to the cyclization process due to its basic properties. All additives could enhance the nucleophilicity of the hydroxyl group of the alkenol and also mediate the stabilization of the oxonium ion intermediates. In the case of alkenols with larger substituents as in **1c**, **1d**, and **1e**, the product yields go down regarding to the effects of steric hindrance. Depending on the mechanism, this can indeed be expected.

Table 1. Phenylselenoetherification of some Δ^5-alkenols in the presence of catalytic amounts of pyridine, Ag_2O, and AgO*Ac*. A $\cdots$ *Ph*SeCl, B $\cdots$ *Ph*SeBr

Substrates	Products	Yields of cyclic ether products/%							
		A	A/*py*	A/Ag_2O	A/AgO*Ac*	B	B/*py*	B/Ag_2O	B/AgO*Ac*
1a	**2a**	81	90	98	86	75	79	86	77
1b	**2b**	80	86	90	83	26	63	78	32
1c	**2c**	31	54	69	35	0	36	55	27
1d	**2d**	33	56	71	40	0	38	59	30
1e	**2e**	30	51	68	34	0	35	54	29

Table 2. Phenylselenoetherification of some Δ^5-alkenols in the presence of equimolar amounts of pyridine, Ag_2O, and AgO*Ac*. A $\cdots$ *Ph*SeCl, B $\cdots$ *Ph*SeBr

Substrates	Products	Yields of cyclic ether products/%							
		A	A/*py*	A/Ag_2O	A/AgO*Ac*	B	B/*py*	B/Ag_2O	B/AgO*Ac*
1a	**2a**	81	100	100	89	75	100	98	80
1b	**2b**	80	100	100	85	26	100	97	62
1c	**2c**	31	100	96	58	0	100	87	42
1d	**2d**	33	100	97	60	0	100	88	45
1e	**2e**	30	93	87	54	0	85	81	40

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

Scheme 1

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 synthesis. Accompanied by other merits, such as the mildness of the reaction conditions and the simplicity of the experimental procedure, our synthesis is the most attractive one for the conversion of alkenols into oxacyclic compounds.

Experimental

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 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.

General Procedure

All reactions were carried out on a 1 mmol scale. To a magnetically stirred solution of 1 mmol of alkenol and 0.1 mmol or 1 mmol of additive in 5 cm^3 of dry CH_2Cl_2 was added 0.212 g of solid *Ph*SeCl (1.1 mmol) or 0.260 g of *Ph*SeBr (1.1 mmol) at room temperature. The reaction went to completion in a

few minutes. The pale yellow solution was washed (in the case of pyridine as additive) with 5 cm^3 of 1 *M* aqueous HCl solution, saturated $NaHCO_3$ solution, and then brine or with saturated $NaHCO_3$ solution and H_2O (in the case of Ag_2O and AgO*Ac*). The organic layer was dried (Na_2SO_4), concentrated, and chromatography was performed. The product was obtained after elution of traces of diphenyl diselenide from a silica gel column using CH_2Cl_2 as eluent. All the products were characterized and identified on the basis of their spectral data. The cyclic ether products are known compounds, and their spectral data have been given previously [29].

Acknowledgments

This work was founded by the Ministry of Science, Technologies, and Development of the Republic of Serbia (Grant: 1254).

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