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Facile pyridine-catalyzed phenylselenoetherification of alkenols

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Abstract

An innovative route for intramolecular cyclization of alkenols has been delineated through a ring closing reaction of suitably alkenols functionalized cyclic ethers tetrahydropyran or tetrahydrofuran type by reaction with phenylselenyl halides, in good yield. Proper choice of some Δ^4- and Δ^5-alkenols and pyridine as catalyst enables fast and facile cyclization. Catalytic amount of pyridine increased the yield, but in the presence of equimolar amount of pyridine, formation of corresponding cyclic ethers were quantitative and reaction were achieved instantaneously under extremely mild experimental conditions. It is possible that aromatic–aromatic ring stacking provides such role of pyridine. The effect of the steric hindrance in the starting alkenols, and halide ion of the selenenylating reagent is not significant, all halides generally giving equal results, and primary, secondary, tertiary and more substituted alkenols also giving quantitative yields.

Keywords: Alcohol; Cyclization; Phenylselenoetherification; Pyridine

1. Introduction

The tetrahydrofuran and tetrahydropyran are not uncommon among biologically active and natural compounds. Cyclofunctionalization of unsaturated alcohols is a very popular reaction providing easy access to tetrahydrofuran and tetrahydropyran cyclic ether products [1–6]. 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 required [5–7]. This methodology has been extended to more complex systems having alcohol and double bond functions.

Cyclization of unsaturated alcohols leading to cyclic ethers is well documented in the literature as convenient pathways in the synthesis of natural products and related compounds [8]. During the last years, cyclic ethers have attracted considerable attention due to their occurrence in several groups of natural compounds exhibiting important biological activities [9]. These units can be found in monocyclic or polycyclic compounds, fused with other cyclic ethers or forming spiro systems [10]. 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 [11–14]. This activity is responsible for their antibiotic [11], neurotoxic [15,16], antiviral [17], and cytotoxic action [18,19] and as growth regulators [11,20,21] or inhibitors of the level of cholesterol in blood [22].

In continuation of our studies on the electrophile-assisted intramolecular cyclization of alkenols [3,23–26] 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 [23]. Intramolecular heterocyclization is the main reaction in the case of all investigated primary and secondary Δ^4-alkenols. PhSeCl has being 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

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are not converted into cyclic products at all by PhSeBr and in a small extent with PhSeCl. The steric influence of substituents is clearly demonstrated in that case.

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. 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. For some time we have been involved in the development and exploration of new methods for cyclofuncionalization of substituted unsaturated alcohols [23–26]. Thus we found that in the presence of pyridine tertiary alkenols cyclized in quantitative yields [24]. Now we explored this method on the primary and secondary alcohols and found the same effect.

2. Experimental

2.1. General methods

GLC analysis were obtained with a Deni instrument, model 2000 with capillary apolar columns. ^{1}H 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. 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.

2.2. Materials

All the olefinic alcohols used as substrates are known compounds, some of which are commercially available, while the other ones were synthesized according to the known procedure. Reagents (PhSeCl and PhSeBr) were used as supplied by Aldrich. Dichloromethane was distilled from calcium hydride.

2.3. General procedure

All reactions were carried out on 1 mmol scale. To a magnetically stirred solution of alkenol (1 mmol) and pyridine (0.0087 g, 0.1 mmol or 0.087 g, 1.1 mmol) in dry dichlomethane (5 cm^3) 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. Pale yellow solution was washed with 1 M HCl aqueous solution (5 mL), saturated $NaHCO_3$ aqueous solution and brine. Organic layer was dried over Na_2SO_4, concentrated and chromatographed. TLC and GLC 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 were given previously [23].

3. Results and discussion

In connection to expanding the generality of catalytic ring-closing reactions, a number of alkenols were subjected by means of phenylselenyl halides (PhSeX, X = Cl, Br) under 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 in vain. We were interested in exploring how PhSeX behave in the presence of some additive and have therefore undertaken a study of the reaction of alkenols with PhSeX (X = Cl, Br) in the presence of base. As it seemed essential to remove HX (Fig. 1), the reactions were performed in the presence of $NaHCO_3$ and triethylamine, but there was not any significant effect on the yield. By adding pyridine in catalytic amount yields of cyclic ethers products increase rapidlly. Finaly, when the reactions were carried out in the presence of equimolar amount of pyridine an instantaneous cyclization occurred and quantitative yields of cyclic ether products were obtained. This seems to be due to the participation of pyridine, which can stabilize episelenonium ion intermediate, but the details are not yet clear.

We describe herein the details of this new procedure. The procedure employs phenylselenyl chloride and bromide, some Δ^4- and Δ^5-alkenols and catalytic or equimolar amount of pyridine to generate an episelenonium ion intermediate from which the cyclic ether product tetrahydropyran or tetrahydrofuran type arise by internal nucleophilic displacement (Fig. 1). The results of our investigation are shown in Tables 1 and 2 and in Figs. 1–4.

As it can be seen from the results obtained the presence of pyridine 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: PhSeX approaches the double bond moiety of the alkenols (**1**) (Fig. 1). Intramolecular capture of the selenonium species (**2**) by an internal hydroxyl nucleophile, which is facilitated by the presence of pyridine, results in the formation of a ring (**3**) and/or (**4**) depending on the structure of starting alkenol.

Primary (**5a**, **5b**) and secondary (**5c**) Δ^4-alkenols with terminal double bond as well as Δ^4-alkenol with terminally

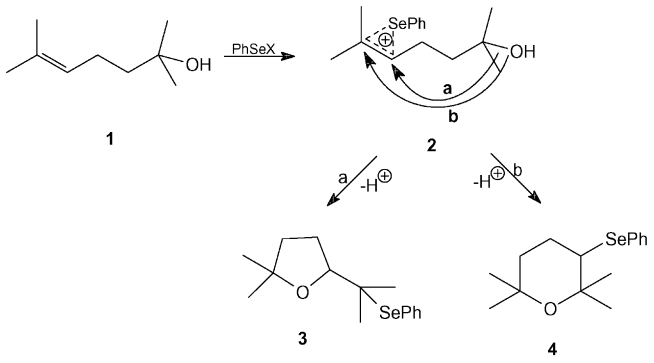


Fig. 1.

Table 1
Phenylselenoetherification of some Δ^4-alkenols in the presence of catalytic and equimolar amount of pyridine, A···PhSeCl, B···PhSeBr

Substrate	Products		Yields of cyclic ethers products (%[a])					
			A	A/py kat.	A/py eq.	B	B/py kat.	B/py eq.
5a	**6a**		69	85	100	63	76	100
5b	**6b**		92	97	100	64	78	100
5c	**6c**		86	94	100	47	55	100
5d	**6d**		72	88	100	75	80	100
5e		**7e**	81	92	100	65	78	100
5f	**6f**		83	95	100	62	75	100
5g		**7g**	61	82	100	55	68	100
5h		**7h**	58	71	100	46	52	100
5i	**6i**	**7i**	37	64	100 (88:12)[b]	0	37	100 (87:13)[b]
5j	**6j**	**7j**	31	61	100 (78:22)[b]	0	35	100 (70:30)[b]
5k	**6k**	**7k**	46	68	100 (86:14)[b]	0	39	100 (84:16)[b]
8	**9**	**10**	34	63	100 (3:97)[b]		30	100 (5:95)[b]

[a] Isolated yields.
[b] Relative distribution of the THF- and THP-type phenylseleno ether products (given in parentheses) was evaluated by capillary GLC and ^{1}H NMR analysis.

Table 2
Phenylselenoetherification of some Δ^5-alkenols in the presence of catalytic and equimolar amount of pyridine, A···PhSeCl, B···PhSeBr

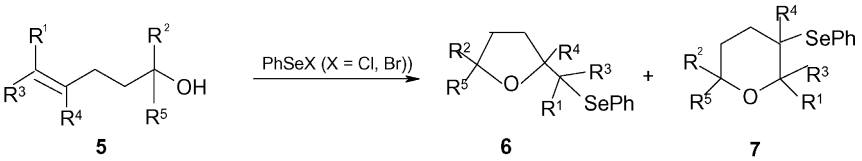
Substrate	Products	Yields of cyclic ethers products (%[a])					
		A	A/py kat.	A/py eq.	B	B/py kat.	B/py eq.
11a	**12a**	81	90	100	75	79	100
11b	**12b**	80	86	100	26	63	100
11c	**12c**	31	54	100	0	36	100
11d	**12d**	33	56	100	0	38	100
11e	**12e**	30	51	93	0	35	85

[a] Isolated yields.

monosubstituted double bond (**5d**, **5f**) afford regioselectively five-membered cyclic ethers (**6a**, **6b**, **6c** and **6d**, **6f**, respectively). Δ^4-Alkenol **5e** with *E*-configuration in contrast to **5d** (*Z*-configuration) affords six-membered cyclic ether **7e** as an unique product (Table 1, Fig. 2).

In the case of primary and secondary Δ^4-alkenols with terminally disubstituted double bond (**5g**, **5h**), PhSe-group adds at the less substituted carbon affording the more stable carbenium ion producing only tetrahydropyran derivatives (**7g**, **7h**; Fig. 2).

Tertiary alkenol (**5i**) with the same substitution at the double bond affords the mixture of six- and five-membered cyclic ethers where five-membered dominate, although the Markovnikoff rule requires that PhSe-group be added at the less substituted carbon to afford the more stable carbenium ion, the reaction is mostly dominated by stereic effects that favours attack of the oxygen at the less substituted carbon, producing as the major products tetrahydrofuran derivative (**6i**, **7i**; 88:12, Fig. 2 and Table 1). Other tertiary alkenols (**5j**, **5k**) also give mixture of



5 **6** **7**

5a $R^1 = R^2 = R^3 = R^4 = R^5 = H$ — 6a — 7a
5b $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = CH_3$ — 6b — 7b
5c $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = CH_3$ — 6c — 7c
5d $R^2 = R^3 = R^4 = R^5 = H$, $R^1 = CH_3$ (Z) — 6d — 7d
5e $R^2 = R^3 = R^4 = R^5 = H$, $R^1 = CH_3$ (E) — 6e — 7e
5f $R^2 = R^3 = R^5 = H$, $R^4 = CH_3$ $R^1 = CH_2CH_3$ — 6f — 7f
5g $R^2 = R^4 = R^5 = H$, $R^1 = R^3 = CH_3$ — 6g — 7g
5h $R^4 = R^5 = H$, $R^1 = R^2 = R^3 = CH_3$ — 6h — 7h
5i $R^4 = H$, $R^1 = R^2 = R^3 = R^5 = CH_3$ — 6i — 7i
5j $R^5 = H$, $R^1 = R^2 = R^3 = R^4 = CH_3$ — 6j — 7j
5k $R^4 = H$, $R^1 = R^2 = R^3 = CH_3$, $R^5 = CH{=}CH_2$ — 6k — 7k

Fig. 2.

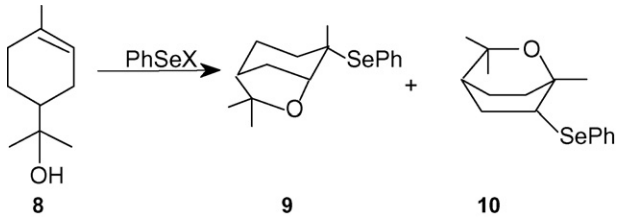


Fig. 3.

five-membered and six-membered ethers but five-membered are the major products. This fact might play an important role in preparation of substituted tetrahydrofurans because of the widespread occurrence among natural products of structures with five-membered ring incorporated oxygen.

Constitutionally similar to the above mentioned Δ^4-alkenols, but cyclic, α-terpineol (**8**) gives mixture of five-membered (**9**) and six-membered ether (**10**) but ether **10** predominate presumably because of electronic and conformational factors (Fig. 3). In the presence of pyridine six-membered product (**10**) is unique product.

As we can see from the Fig. 2 and Table 1 alcohols **5k** and **8** (linalol and α-terpineol) give the products, which can be easily transformed in the natural products karahaneone [27] and cineol [28] in excelent yields.

In this paper, we also present the extension of the methodology to some primary, secondary and tertiary Δ^5-alkenols. 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 would readily be accomplished in synthetically useful yields, regardless of the reagent used. The results of our investigation are shown in Table 2 and Fig. 4.

All reactions proceeded to form six-membered oxygen heterocycles bearing the phenylselenomoiety. It 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. Yields of products are higher and reaction time is 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 in the case of an equimolar amount. In the case of alkenols with larger substituents as in **11d** and **11e** (Fig. 4, Table 2) the product yields are also high regardless of the effects of steric hindrance. Only alkenol **11e** with two double bonds reacts a little bit worse than other alkenols probably because of presence of another double bond to which reagent can add and give a small amount of addition product. Depending on the mechanism, this can indeed be expected.

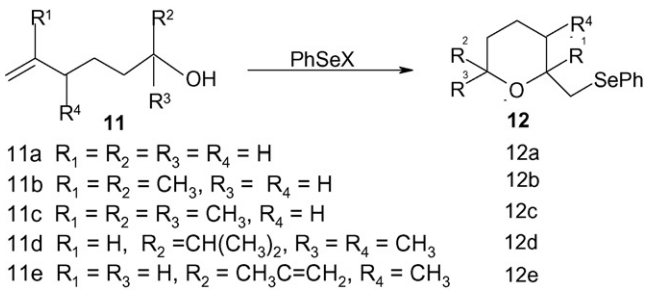


Fig. 4.

4. Conclusion

In conclusion, above results clearly indicate that there is no difference in reactivity between PhSeCl and PhSeBr in the presence of equimolar amount of pyridine (Tables 1 and 2). As far as we know it is the first example where these two reagents have the same behavior. PhSeBr is known to be superior reagent only for effecting intramolecular amidoselenenylations of *N*-alkenylamides [29]. Previous results obtained in the reactions of alkenols with PhSeX indicate that PhSeCl is more efficient reagent for cyclization than PhSeBr [23]. 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 oxonium ion intermediates by abstracting the hydrogen (Fig. 1). It seems that pyridine could play several roles. One of the possible explanation may be for the case of $\pi\cdots\pi$ interactions. It is possible that such role of pyridine can be explains by aromatic-aromatic ring stacking. Ring stacking provides the stabilising interaction in the intermediate and in transition state by ctacking of aromatic ring of reagent (PhSeX) on aromatic ring of pyridine which is well documented in the literature [30–33]. 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 unsubstituted and substituted tetrahydrofuran and tetrahydropyran derivatives, but also opens a new area involving the use of pyridine as catalyst in cyclization reactions.

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