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ORIGINAL PAPER

Cyclization of some terpenic alcohols by phenylselenoetherification reaction

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Abstract Highly substituted tetrahydrofuran (THF)- and tetrahydropyran (THP)-type rings are formed through an acid- or base-catalyzed 5-*exo* and/or 6-*endo* cyclization of some natural terpenic alcohols (e.g., linalool, nerolidol, and α-terpineol) by an electrophile-mediated cyclization with PhSeCl and PhSeBr. The side chains of these cyclic ether products can be further transformed easily into a wide range of substrates owing to the versatile functionality of the double bond. Certain regioselectivity was noticed in these reactions. Nerolidol behaves like linalool in the reaction with PhSeX and affords predominantly THF derivatives, whereas α-terpineol affords THPs. Some Lewis bases (triethylamine, pyridine, 2,2′-bipyridine, and quinoline) and Lewis acids ($SnCl_2$ and $CoCl_2$) were used as additives, the presence of which increases the yields from 5–40 % to almost quantitative.

Keywords Alcohol · Cyclization · Lewis acids · Lewis bases

Introduction

Applications of selenium reagents in organic chemistry have developed rapidly over the past few decades. Perhaps the most important usage of electrophilic selenium reagents is in selenocyclization reactions. Selenocyclizations constitute a subset of the class of reactions termed cyclofunctionalizations [1], in which electrophilic addition to a double bond triggers capture of the resulting intermediate by a pendant nucleophilic group to generate a cyclic product. The first example of a selenocyclization was reported in 1960 [2] and involved the formation of a selenolactone from an unsaturated carboxylic acid. These reactions were extensively developed in the 1970s [3–6] and became useful tools in organic synthesis because of the further elaboration of the resulting selenides to alkenes (via oxidation and elimination) or to addition products (via radical chemistry) [7, 8]. The versatility of these reactions is enhanced by the wide range of pendant nucleophiles that can be utilized in these reactions. For example, carboxylic acids, alcohols, amines, amides, enol ethers, and vinylstannanes have all been employed as nucleophiles in selenocyclization reactions [9–11]. This represented the first useful application of selenium derivatives in organic synthesis and led to the development of new methods and reagents that are now used routinely in synthetic organic chemistry. Not surprisingly, these reactions have also found widespread use in natural product synthesis [12]. In particular, selenoetherification reactions have been used in the preparation of prostaglandin analogues [13, 14]. Substituted tetrahydrofuran (THF) and tetrahydropyran (THP) ring systems are common structural units found in many bioactive natural products [15]. Consequently, the development of strategies for the stereocontrolled synthesis of substituted THFs and THPs is an area of considerable ongoing interest [16]. For some time we have been involved in the development and exploration of new methods for cyclofunctionalization of unsaturated alcohols [17–19]. Herein, we report the cyclization of linalool (**1**), nerolidol (**2**), and α-terpineol (**3**) by the action of phenylselenenyl chloride and bromide in dichloromethane. These alcohols are naturally occurring terpenic alcohols

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found in the volatile oils obtained from various flowers, fruits, grasses, leaves, roots, seeds, and woods. Some research has been published on their antiviral, antibacterial, antimicrobial, and potential antitumor and anticancer effects [20–23]. On the other hand, some cyclization products of these alcohols (like cineol which is made from α-terpineol) also have some effects on human health.

Results and discussion

The starting point for this investigation was to prepare the selenoether products derived from some terpenic alcohols and to establish the proper reaction conditions required for their preparation using benzeneselenenyl chloride and benzeneselenenyl bromide as a reagent. The side chains of these cyclic ether products can be further transformed easily into a wide range of substrates owing to the versatile functionality of the double bond. As a part of our continuing interest to develop new concepts of catalysis for cyclization reactions of unsaturated alcohols we investigated the use of Lewis acids and bases. Some aliphatic and aromatic amines were used as Lewis base additives [triethylamine (Et_3N), pyridine (Py), 2,2′-bipyridine (BiPy), and quinoline (Qui)] and some salts as Lewis acid additives ($CoCl_2$, $SnCl_2$). The presence of additives increases the yields from 5–40 % to almost quantitative. Also, the additive caused a dramatic increase in the reaction rate. All reactions were finished within a few minutes (without additives the reaction time 0.5 h to several hours).

The results of our investigation are summarized in Tables 1 and 2 and Schemes 1 and 2. All reactions proceeded in high yields with the formation of an oxygen heterocycle bearing the phenylseleno moiety. The presence of additives increases the yields of cyclic ether products to almost quantitative in the case of all three alkenols, whereas the side reaction, addition of PhSeX to the double bond of the starting material, is reduced to a minimum. In the absence of additive, this direct addition of the reagent to the double bond is the main reaction.

The results in Tables 1 and 2 indicate certain regioselectivity in these reactions. In the reaction with PhSeX (X = Cl, Br) nerolidol behaves like linalool and affords predominantly THF derivatives, whereas α-terpineol affords only THPs. The cyclization of α-terpineol is regiospecific and produces only six-membered ring systems. Nerolidol gives only five-membered ring systems in all reactions except with 2,2′-bipyridine as an additive with both reagents and quinoline with PhSeBr as a reagent. The lowest regioselectivity was in the cyclization of linalool. In all cases the THF-type ring forms in high excess, but there is also a six-membered ring present. The lowest selectivity was with triethylamine/PhSeCl and quinoline/PhSeBr systems, whereas the pyridine/PhSeBr system gives only one THF-type ring.

The distribution of cyclic ethers depends on the specific additive used. The role of Lewis acids in these reactions is to increase the electrophilicity of the reagent (PhSeX) and to decrease the possibility of addition of halides by removing the anion from the reagent and in that way improving yields of the desired products. The possible role of Lewis bases is to enhance the nucleophilicity of the oxygen in the hydroxyl group of the alkenol by formation of a hydrogen bond, and to remove the proton facilitating the formation of the final product.

On the basis of the results from this research it can be concluded that the cyclizations of linalool and nerolidol are under kinetic control, whereas the cyclization of α-terpineol is under thermodynamic control, probably because of the rigidness of its cyclic system.

Although the cyclizations of linalool and nerolidol show very high regioselectivity, this is not the case with stereoselectivity. The distributions of *cis* and *trans* isomers of the THF products **1a** and **2a** are shown in Table 3. With linalool the ratio of *cis*/*trans* products in **1a** varies with the additive used regardless of which Lewis acid or base additive is used. The *cis*/*trans* ratio in the nerolidol-derived product **2a** is shifted in favor of the *cis* isomer.

These developments in base- and acid-catalyzed cycloselenoetherification clearly demonstrate that these strategies can be used to facilitate the functionalization of different substrates for construction of O-heterocycles. 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 the facile synthesis of various heterocycles.

Experimental

GC analysis were obtained with an Agilent Technologies instrument (model 6890 N) with HP-5NS columns (5 % phenyl-, 95 % methylpolysiloxane). ^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 & Kolbe and found to be in good agreement with the calculated values [24]. 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. Terpenic alcohols used as starting materials are commercially available. Reagents

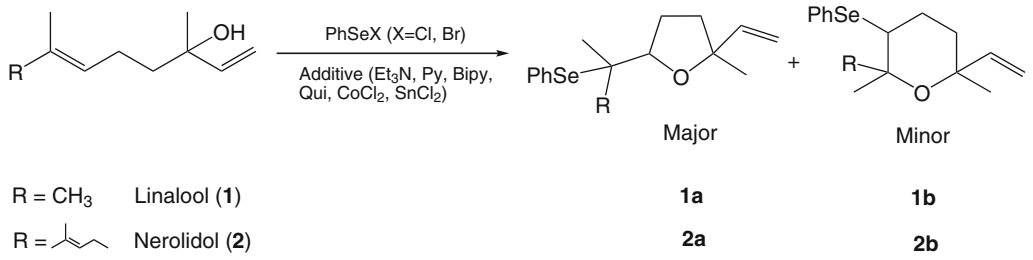
Table 1 Phenylselenoetherification of some Δ^4-terpenic alkenols with PhSeCl in the presence of equimolar amounts of Lewis acids and bases

Substrate	Products	Yields and ratio (a:b) of cyclic products/%					
		Et_3N	Py	Qui	Bipy	$SnCl_2$	$CoCl_2$
1	**1a**, **1b**	100 (81:19)	93 (93:7)	96 (97:3)	94 (96:4)	86 (94:6)	75 (95:5)
2	**2a**, **2b**	100 (100:0)	100 (100:0)	99 (100:0)	98 (94:6)	100 (100:0)	100 (100:0)
3	**3a**, **3b**	100 (0:100)	99 (0:100)	100 (0:100)	100 (0:100)	100 (0:100)	91 (0:100)

Table 2 Phenylselenoetherification of some Δ^4-terpenic alkenols with PhSeBr in the presence of equimolar amounts of Lewis acids and bases

Substrate	Products	Yields and ratio (a:b) of cyclic products/%					
		Et_3N	Py	Qui	Bipy	$SnCl_2$	$CoCl_2$
1	**1a**, **1b**	67 (94:6)	87 (100:0)	81 (63:37)	96 (95:5)	92 (96:4)	72 (95:5)
2	**2a**, **2b**	98 (100:0)	100 (100:0)	100 (97:3)	99 (92:8)	100 (100:0)	100 (100:0)
3	**3a**, **3b**	100 (0:100)	100 (0:100)	95 (0:100)	100 (0:100)	100 (0:100)	100 (0:100)

Scheme 1



Scheme 2

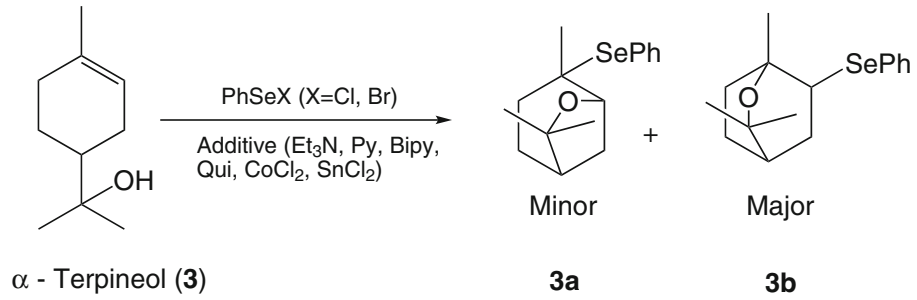


Table 3 Ratio of *cis* and *trans* isomers in products **1a** and **2a**

Ether	Reagent	Ratio (*cis*:*trans*) of cyclic products/%					
		Et_3N	Py	Qui	BiPy	$SnCl_2$	$CoCl_2$
1a	PhSeCl	26:74	51:49	39:61	52:48	36:64	60:40
	PhSeBr	36:64	59:41	61:39	54:46	40:60	13:87
2a	PhSeCl	80:20	65:35	73:27	88:12	70:30	88:12
	PhSeBr	77:23	85:15	68:32	71:29	78:22	81:19

(PhSeCl and PhSeBr) were used as supplied by Aldrich. Dichloromethane was distilled from calcium hydride.

General experimental procedure

All reactions were carried out on a 1-mmol scale. To a magnetically stirred solution of 1 mmol of alkenol (0.154 g of α-terpineol and linalool or 0.222 g of nerolidol) and 0.101 g Et_3N or 0.19 g $SnCl_2$ or 0.156 g BiPy or 0.079 g Py or 0.129 g quinoline or 0.065 g $CoCl_2$ (0.5 mmol) in 5 cm^3 dry dichlomethane was added 0.212 g solid PhSeCl (1.1 mmol) or 0.260 g PhSeBr (1.1 mmol) at room temperature until the solid dissolved. The reaction went to completion virtually instantaneously. The resulting pale yellow solution was washed with 2 M HCl (only in the case with bases as additives), then saturated $NaHCO_3$ aqueous solution, and brine. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed. TLC and GC analysis as well as NMR spectra showed complete conversion of starting alkenol to cyclic ether product. The product was obtained after the elution of the traces of diphenyl diselenide on a silica gel column with dichloromethane.

cis- and trans-5-Ethenyl-5-methyl-2-[2-(phenylseleno)-prop-2-yl]tetrahydrofuran (**1a**, $C_{16}H_{22}OSe$)
^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.31$ (s, 3H, CH_3-6), 1.33 and 1.36 (2 s, 2 × 3H, $C(CH_3)_2$), 1.55–2.12 (m, 4H, H-3 and H-4), 3.94 (m, 1H, H-2), 4.98 (dd, 1H, $J_{Hz\text{-}8,H\text{-}7} \approx 9$ Hz, $J_{Hz\text{-}8,He\text{-}8} \approx 1$ Hz, H_z-8), 5.18 (dd, 1H, $J_{He\text{-}8,H\text{-}7} \approx 12.6$ Hz, $J_{He\text{-}8,Hz\text{-}8} \approx 1$ Hz, H_e-8), 5.86 (dd, 1H, $J_{H\text{-}7,He\text{-}8} \approx 12.6$ Hz, $J_{H\text{-}7,Hz\text{-}8} \approx 9$ Hz, H-7), 7.25 (m, 3H, H_{Ph}), 7.67 (m, 2H, H_{Ph}) ppm; ^{13}C NMR (50.32 MHz, $CDCl_3$,): $\delta = 25.61$ (CH_3, C-6), 25.8 and 26.31 (CH_3, C-10), 26.53 and 26.67 (CH_3, C-9), 27.71 and 27.84 (CH_2, C-3), 37.13 and 37.76 (CH_2, C-4), 49.49 and 49.68 (C, C-11), 82.72 and 83.01 (C, C-5), 85.26 and 85.55 (CH, C-2), 111.12 and 111.15 (CH_2, C-8), 127.23 and 127.26 (C, C-12), 128.25 and 128.29 (CH, C-14), 128.35 and 128.41 (CH, C-15), 138.37 (CH, C-13), 143.59 and 144.01 (CH, C-7) ppm.

cis- and trans-5-Ethenyl-5-methyl-2-[6-methyl-2-(phenylseleno)hept-5-en-2-yl]tetrahydrofuran (**2a**, $C_{21}H_{30}OSe$)
cis-**2a**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.23$ (s, CH_3Se), 1.28 (s, CH_3CO), 1.62 and 1.68 (2 s, $(CH_3)_2C$=), 1.65–1.71 (m, CH_2CO), 1.71–2.05 (m, CH_2CSe, CH_2CHO), 2.08–2.33 (m, CH_2CH=), 3.99 (t, $J = 7.3$ Hz, CHO), 4.98 (dd, $J = 1.5$ Hz, 10.8 Hz, CH=CH), 5.08 (tq, $J = 1.4$ Hz, 7.1 Hz, CH=$C(CH_3)_2$), 5.22 (dd, $J = 1.5$ Hz, 17.4 Hz, CH=CH), 6.0 (dd, $J = 6.7$ Hz, 10.8 Hz, CH=CH_2), 7.18–7.32 (m, *o*-, *p*-CH), 7.6–7.71 (m, *m*-CH) ppm; ^{13}C NMR (50.32 MHz, $CDCl_3$): $\delta = 17.71$ and 22.95 ($(CH_3)_2C$=), 24.02 (CH_2CHO), 25.68 (CH_3CSe), 26.82 (CH_3CO), 27.74 (CH_2CH=), 37.87 (CH_2CO), 38.71 (CH_2CSe), 54.75 (CSe), 82.54 (CO), 84.31 (CHO), 111.32 (CH_2=), 124.35 (CH=$C(CH_3)_2$), 127.68 (=CSe), 128.41 (*p*-CH), 129.13 (*m*-CH), 131.45 (=$C(CH_3)_2$), 138.49 (*o*-CH), 144.15 (CH=CH_2) ppm.

trans-**2a**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.21$ (s, CH_3Se), 1.33 (s, CH_3CO), 1.62 and 1.68 (2 s $(CH_3)_2C$=), 1.65–1.71 (m, CH_2CO), 1.71–2.05 (m, CH_2CSe, CH_2CHO), 2.08–2.33 (m, CH_2CH=), 3.97 (t, $J = 10.9$ Hz, CHO), 4.97 (dd, $J = 1.5$ Hz, 10.8 Hz, CH=CH), 5.08 (tq, $J = 1.4$ Hz, 7.1 Hz, CH=$C(CH_3)_2$), 5.13 (dd, $J = 1.5$ Hz, 17.4 Hz, CH=CH), 5.86 (dd, $J = 6.7$ Hz, 10.8 Hz, CH=CH_2), 7.18–7.32 (m, *o*-, *p*-CH), 7.6–7.71 (m, *m*-CH) ppm; ^{13}C NMR (50.32 MHz, $CDCl_3$): $\delta = 17.71$ and 22.95 ($(CH_3)_2C$=), 24.02 (CH_2CHO), 25.58 (CH_3CSe), 27.74 (CH_2CH=), 28.02 (CH_3CO), 37.09 (CH_2CO), 38.98 (CH_2CSe), 55.02 (CSe), 82.99 (CO), 84.50 (CHO), 111.14 (CH_2=), 124.35 (CH=$C(CH_3)_2$), 127.55 (=CSe), 128.21 (*p*-CH), 128.26 (*m*-CH), 131.45 (=$C(CH_3)_2$), 138.43 (*o*-CH), 143.80 (CH=CH_2) ppm.

6-(Phenylseleno)-1,3,3-trimethyl-2-oxabicyclo [2.2.2]octane (**3b**, $C_{16}H_{22}OSe$)
IR (KBr): $\bar{\nu} = 2{,}967$, 2,927, 1,633, 1,577, 1,475, 1,378, 982 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.11$ (s, 3H, CH_3CO), 1.23 and 1.25 (2 s, 2 × 3H, $(CH_3)_2CO$), 1.42–1.80 (m, 4H, H-5, H-8), 1.90–2.14 (m, 2H, H-7), 2.62 (tt, 1H, $J = 3.3$ Hz, 7.7 Hz, H-4), 3.52 (dd, 1H, $J = 2.6$ Hz, 5.9 Hz, H-6), 7.20–7.29 (m, 3H, H_{Ph}), 7.51–7.59 (m, 2H, H_{Ph}) ppm; ^{13}C NMR (50.32 MHz, $CDCl_3$): $\delta = 22.21$ (CH_3CHC), 26.84 (CH_3CO), 27.73 (CH_2CHSe), 28.48 and 28.90 ($(CH_3)_2CO$), 33.98 (CH_2CO), 34.38 (CHC), 45.61 (CHSe), 73.74 (CCH_3CO), 73.91 ($C(CH_3)_2CO$), 127.12 (*p*-CH), 128.96 (*m*-CH), 130.59 (=CSe), 133.78 (*o*-CH) ppm; MS (70 eV): $m/z = 310$ $[M]^+$, 184, 153, 109, 77, 43.

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