

A Simple, Convenient and Expeditious Approach to Cineol

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ABSTRACT: A convenient two-step protocol preparation of cineol (1-isopropyl-4-methyl-7-oxabicyclo-[2,2,1]heptane) from α -terpineol (*p*-menth-1-en-8-ol) is reported. The phenylselenoetherification of α -terpineol with PhSeX ($X = Cl, Br, I$) as a key step is described. α -Terpineol reacts with PhSeX to form the corresponding phenylselenoether in short reaction time and in quantitative yield. A subsequent reduction with Bu_3SnH to cineol proceeds in high yield (98%) © 2004 Wiley Periodicals, Inc. *Heteroatom Chem* 15:468–470, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20044

INTRODUCTION

Cyclofunctionalization of unsaturated alcohols is a very popular reaction providing easy access to 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 system 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 past 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 the past few years, attention has been focused on the synthesis of the substituted tetrahydropyrans and tetrahydrofuranes as key starting materials for the preparation of numerous heterocyclic compounds including physiologically active products. Tetrahydropyrans 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 [11]. Hence, of particular importance is the discovery of the appropriate experimental conditions under which phenylselenocyclization of alkenols would readily be accomplished in synthetically useful yields, regardless of the reagent used. This prompted us to examine a methodology for the synthesis of these systems. In recent years, we have studied intramolecular cyclization of some Δ^4 - and Δ^5 -alkenols by means of

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phenylselenenyl halides [23], PhSeX (X = Cl, Br). 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 PhSeBr and in a small amount with PhSeCl.

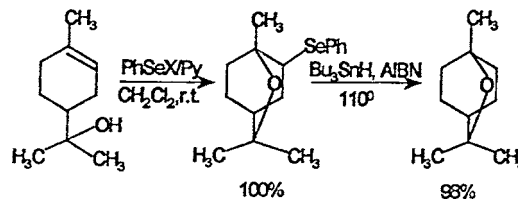
RESULTS AND DISCUSSION

Recently, we presented an approach to cyclic ethers from tertiary alkenols using PhSeX (X = Cl, Br) in the presence of pyridine [24]. The procedure works smoothly resulting in quantitative formation of the cyclic ethers. Prompted by this finding, we considered it synthetically interesting and profitable for our purposes to extend this method to other representative alkenols in order to describe a general procedure for a rapid and efficient cyclization reaction of alkenols with phenylselenenyl halides [25,26]. Various substituted tetrahydrofuran and tetrahydropyran rings were obtained that depended on the structure of the starting alkenols. Oxidative or reductive elimination of phenylseleno group gave different unsaturated or saturated ethers that are constituents of many natural and biological active products. In particular, our attention focused on the development of a general synthetic route for the preparation of cineol. It is a matter of fact that cineol (eucalyptol) has a widespread use (in cough syrups and expectorants, in perfumery, and flavoring). Available methods for the preparation of cineol require more steps in the synthetic process with unsatisfactory yields [27,28], or isolation from natural products [29]. The most common approach involves phenylselenoetherification of α -terpineol and a subsequent reduction with Bu_3SnH or by catalytic hydrogenation (H_2 , Pd/C, or Ra/Ni in THF at room temperature).

The cyclization step was carried out by addition of 1 equivalent of PhSeX (X = Cl, Br, I) at room temperature to a CH_2Cl_2 solution of α -terpineol and pyridine (in ratio 1:1), and cyclic ether bearing PhSe group was obtained in quantitative yield (100%). Reduction of this cyclic ether (elimination of PhSe group) with Bu_3SnH in toluene at 110°C in the presence of AIBN gave a 98% yield of the cineol (see Scheme 1). When the removing of PhSe group was performed by catalytic hydrogenation with Ra/Ni in THF at room temperature, the yield of cineol was lower (94%).

EXPERIMENTAL

All reactions were carried out on a 1 mmol scale. To a magnetically stirred solution of alkenol (1 mmol)



SCHEME 1

and pyridine (1 mmol) in dry CH_2Cl_2 (5 cm^3) was added solid PhSeCl (1.1 mmol, 0.212 g) or PhSeBr (1.1 mmol, 0.260 g) or PhSeI (1.1 mmol, 0.311 g) at room temperature. The reaction was completed in few minutes. The pale yellow solution was washed with 5 cm^3 1 M HCl aqueous solution, saturated NaHCO_3 , and then brine. The organic layer was dried (Na_2SO_4), concentrated, and chromatography was performed. The product was obtained after the elution of the traces of diphenyl diselenide from a silica gel/ CH_2Cl_2 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 in the literature [30]. Reduction was performed according to the procedure described earlier [31].

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