Reactivity of the Monoterpenoid Nerol with p-Toluenesulfonic and Chlorosulfonic Acids: Selective Syntheses of α-Terpineol and α-Cyclogeraniol

An Activity for the Undergraduate Organic Lab

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The monoterpenoids are a large group of naturally occurring compounds that have mainly been isolated from higher plants, algae, marine organisms, insects, and some vertebrate animals (1). Members of this chemical family have been used since antiquity in herbal and folk medicine, for food flavoring and preservation, and as ingredients of perfumes and soaps (1–3). Although monoterpenoids would provide good examples for structure elucidation and mechanistic studies, the undergraduate curriculum rarely provides a chance to study this fascinating group of natural products (1).

In this article we describe the use of the monoterpenoid nerol as starting material in the selective synthesis of the cyclic monoterpenes α-terpineol, 1, and α-cyclogeraniol, 4. α-Terpineol, 1, is the main product when p-toluenesulfonic acid (p-TsOH) is used as a reagent and α-cyclogeraniol, 4, is the main product when the superacid chlorosulfonic acid (HSO₃Cl) is used as a reagent (Scheme I). The products in both reactions are produced in sufficient quantities for spectral analyses by ¹H NMR, ¹³C NMR, and MS. The different cyclization pattern of nerol under diverse experimental conditions, such as difference in the acid strength of the cyclizing agents, polarity of the solvents, or reaction temperature, is an ideal opportunity for students of upper-undergraduate level to explore the mechanistic aspects of carbocation chemistry. In fact, our third-year chemistry students, with some previous training in organic synthetic labwork, have carried out these microscale procedures for several years with satisfactory results.

Students treat a quantity of nerol under specific experimental conditions. However, first, it is advisable for students to elucidate the structure of nerol by spectroscopic methods. Then, they must choose the most convenient method to check the reaction progress, to quench the reaction, and to isolate and spectroscopically analyze the resulting compounds. The lab can be completed in one 4-hour period or two shorter periods.

The processes described herein are within the widely used synthetic strategy based on the biomimetic cyclization of terpene derivatives (4, 5). A variety of electrophilic reagents have been described that allow these cyclizations, such as the proton (6), Lewis acids (7–9), or even superacids (10–12). In the field of the electrophilic polyene cyclization methodology the authors have some previous contributions (13–15).

The reaction of nerol with p-toluenesulfonic acid is conducted at room temperature in a stirred solution of nitromethane (experiment 1) or dichloromethane (experiment 2). The reaction of nerol with chlorosulfonic acid is carried out at low temperature in 2-nitropropane under argon (experiment 3), using standard microscale glassware, needles, syringes, and other common lab equipment (Scheme I). The first two experiments are monitored by TLC or GC and a typical reaction time is ca. 1 h, while the third experiment is complete in 10 minutes.

Experimental Procedure

Materials and Reagents

Standard lab equipment is needed for experiments 1 and 2. A standard microscale glassware kit, including a dry 10-mL Luer lock glass syringe, a 2-mL Luer tip plastic syringe, and several long metal needles for transferring liquid, is required for experiment 3. Rubber septa, balloons with needle...
adapters for holding inert atmospheres, several short needles for introducing and venting inert gas, a low-form Dewar flask for the cooling bath, and a low-temperature thermometer are also needed for experiment 3.

Experiments 1 and 2

To a stirred solution of nerol (200 mg, 1.29 mmol) in MeNO₂ or CH₂Cl₂ (10 mL) was added p-TsOH·H₂O (45 mg, 0.23 mmol) at room temperature. The reaction was monitored with TLC or GC. After 0.5–1 h the reaction was quenched with base (5 mL of a saturated aqueous NaHCO₃ solution) and extracted with Et₂O (experiment 1) or CHCl₃ (experiment 2). The crude materials were recovered and analyzed by GC, yielding 80–85% α-terpineol for experiment 1 or 18–22% α-terpineol, 35–40% limonene, and 43–46% terpinolene for experiment 2.

Experiments 3

Nerol (400 mg, 2.58 mmol) and i-PrNO₂ (10 mL) were placed into a pear-shaped flask and kept at low temperature (ca. -80 °C, N₂(l)–EtOAc bath) under argon atmosphere. i-PrNO₂ (4 mL) and HSO₃Cl (1.4 mL, 22.74 mmol) were placed in a round-bottom flask with magnetic stirring and kept at low temperature under argon atmosphere. The nerol solution, previously cooled, was added dropwise with a syringe to the acid solution over a period of 5 min. The mixture was then stirred for an additional 5 min, quenched with base (5 mL of a saturated aqueous NaHCO₃ solution), and extracted with Et₂O. The crude material was recovered and analyzed by GC, yielding 80–85% α-cyclogeraniol.

Hazards

The reactions should be carried out in an efficient hood. Standard precautions should be used when handling and disposing of organic solvents, since potential symptoms of overexposure to dichloromethane are fatigue, weakness, sleepiness, numbness or tingling of limbs, among others, and solvents nitromethane and nitropropane are flammable, toxic, and cancer suspect agents. p-Toluenesulfonic acid is a highly toxic oxidizing agent and is irritating to the skin and mucous membranes. Gloves, goggles, and protective clothing should be worn. Chlorosulfonic acid is a strong acid and causes severe chemical burns if in contact with skin. It reacts violently with moisture releasing HCl and H₂SO₄. Some monoterpenoids, such as limonene, have been described as sensitizers. No other cautions for the rest of monoterpenoids used or obtained here are remarkable.

Results and Discussion

Reaction of nerol with p-toluenesulfonic acid in nitromethane at room temperature yielded α-terpineol, 1, in ca. 85% yield (experiment 1). However, the treatment of nerol with p-toluenesulfonic acid in dichloromethane at room temperature did not only yield 1 but the two isomer hydrocarbons limonene, 2, and terpinolene, 3, as well (1:2:3 ca. 20%:35%:45%, experiment 2). On the other hand, the treatment of nerol with chlorosulfonic acid in 2-nitropropane at low temperature yielded only α-cyclogeraniol, 4, in 80–85% yield (experiment 3).

Owing to the different acid strengths of p-toluenesulfonic and chlorosulfonic acids, the reaction progress is different. A possible explanation to this behavior could be postulated (as not proven by experiment) as follows. The nerol molecule is able to trap protons through the unshared pairs of electrons of the hydroxyl oxygen and the electrons of the two π bonds. When the weaker p-toluenesulfonic acid reacts with nerol, the protons react only with the comparatively more basic hydroxyl group whereas the stronger chlorosulfonic acid can supply protons even to the less basic double bonds (see below). It seems to account for the nature of the carbocation intermediates initially formed and their evolution toward the corresponding final products. In the case of experiments 1 and 2 (p-TsOH), although no mechanistic data are available and so narrowing the choice down to one option is impossible, the reaction could be initiated by the protonation of the hydroxyl group, loss of water, and the intramolecular capture of the allyl cation. Then, the evolution of the resulting p-methane cation by capturing water (path a) or by eliminating adjacent protons (paths b and c) give the cyclic monoterpenoids 1, 2, and 3, in different quantities (Scheme II).

It is worthy to note that the use of p-TsOH in different solvents (nitromethane or dichloromethane) clearly alters the final product ratio. This peculiar outcome might be accounted for by the different ability of both solvents to accommodate water. Thus, the higher solubility of water in nitromethane implies that water is always in the reaction medium, and, hence, water is available to be involved in the mechanism of this cationic cyclization (path a). On the contrary, water is insoluble in dichloromethane, which means...
that water is barely present in the reaction medium, and, accordingly, the needed stabilization of the \( p \)-menthane carbocation has to go mainly through the loss of a proton from adjacent carbon atoms (paths b and c, Scheme II).

On the other hand, chlorosulfonic acid (experiment 3) is a stronger acid and although it is well known for its ability in catalyzed dehydrations (16), it is also known that when used in large excess at low temperature (15) it can establish a superacid medium similar to that of \( \text{HSO}_3\text{F} \) (10–12). In these particular experimental conditions, alkyl cations can be easily formed from olefins, whereas primary and less reactive secondary alcohols are protonated with slow exchange rates (11). Therefore, owing to the temperature dependence of the dehydration kinetics of protonated alcohols in superacid medium (17), the behavior of nerol in these conditions is dramatically different from that of \( \text{p}-\text{toluenesulfonic acid} \) at room temperature. In the former case, the reaction seems to be initiated (Scheme III) by a selective \( \Delta^4 \) protonation of nerol and the intramolecular capture of the tertiary cation. Then, regioselective proton elimination in the resulting cyclic tertiary cation finally gives \( \alpha \)-cyclogeraniol, 4. It has been suggested for related compounds (4a) that the hydroxyl group could function as an internal base for proton removal, justifying the observed regioselective formation of only the \( \alpha \)-isomer 4. However, whether the favored process is a concerted cyclization–elimination step or two steps is still in doubt and should be left as a pedagogically useful open question for the students.

Conclusions

These experiments present a good approach for the study of carbocation chemistry in the advanced undergraduate organic synthesis laboratory. They provide an opportunity to discuss acids, cyclizations, and reactions that involve “true” carbocations; the stability and structure, generation and fate of them, and solvent and temperature effects in the organic chemistry context. The experiment can easily take place in two sessions and, since there are relatively few references to lab experiments for students that address carbocation mechanisms, these experiments could be useful for teaching.

### Supplemental Material

The full description of these experiments with materials and reagents required, detailed experimental procedures, spectra and assignments, further explanations on biomimetic cyclizations and carbocation chemistry, more experimental tasks to supplement the described procedures, notes and tips for the instructor and questions for students, among other helpful material, are available in the issue of JCE Online.

### Literature Cited