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Preparation and utilization of perillyl acetate

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Abstract Perillyl acetate is a fragrance compound that was prepared by the reaction of β-pinenoxide with acetic anhydride and using acetic acid as an acid catalyst. Several selected catalysts were tested (homogenous: phosphoric acid, boric acid, acetic acid, and citric acid; heterogeneous: zeolite USY, SSA, and montmorillonite K-10) and the reaction conditions optimized for this reaction. The yield 78.7 % of perillyl acetate was obtained. Mayol (4-isopropylcyclohexylmethanol), a valuable fragrance compound, was further obtained by a two-step synthesis from perillyl acetate. Firstly, perillyl acetate was saponified to perillyl alcohol. The yield of alcohol was 94.4 %. The last step of the entire preparation was the hydrogenation of perillyl alcohol to Mayol. The yield of the desired product of this reaction was 94.6 %.

Keywords β-pinenoxide · Perillyl acetate · Perillyl alcohol · Cis-4-isopropylcyclohexylmethanol (Mayol)

Introduction

Perillyl acetate is a fragrant compound whose use has been suggested especially in perfumery, in particular as a modifier to selected essential oils (Bergamot, etc.) [1]. It is characterized by a spicy herbal odor suggestive of spearmint, whereas, in a suitable dilution, it has a refreshing, fruity note. Perillyl acetate has also been used in flavor compositions, mainly as a component of artificial spearmint and in spice and condiment flavor blends.

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The starting material for the preparation of perillyl acetate can be β-pinenoxide [2, 3], limonene [4, 5], pinocarveol [6, 7], or some other substances [8–10]. The compound can be prepared by the reaction of β-pinenoxide with acetic anhydride in dichloromethane as a solvent and with montmorillonite K-10 as an acid catalyst [3]. Alternatively, it can be prepared by the reaction with sodium acetate, acetic acid, and Amberlite (IRC-50) [2], obtaining p-ment-1-en-8-acetoxy-7-ol, which yields perillyl acetate under vacuum thermolysis. Methods starting from other substances resulted in lower yields of perillyl acetate, e.g., only up to 40 % using 4-(2-hydroxy-2-propyl)cyclohexene-1-methyl acetate as the starting material [9]. In general, the simplest method for the preparation of perillyl acetate is the reaction of β-pinenoxide with acetic anhydride in the presence of an acid catalyst.

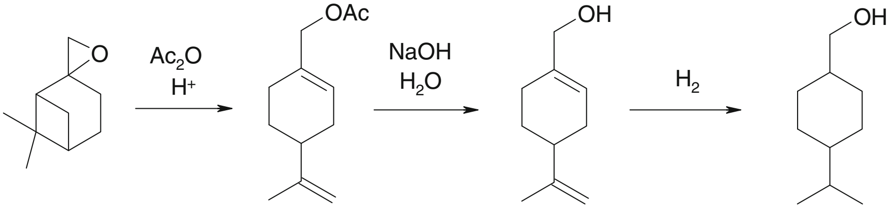
The use of perillyl acetate has certainly not been limited only to the perfume chemistry as it has also been used as the starting material in preparations of other valuable specialty chemicals. However, perillyl alcohol also belongs to the most interesting products prepared from perillyl acetate, owing to its antimicrobial and antineoplastic activity [2] (for the treatment of breast, pancreas, lung, and colon carcinomas). Perillyl alcohol has also been used as the initial substance for the preparation of a high demand fragrance compound, i.e., 4-isopropylcyclohexylmethanol, the so-called Mayol.

The main aim of this work was finding the most effective method for the preparation of perillyl acetate from β-pinenoxide. The reaction system and conditions were optimized. The tested catalysts were selected based on former experience. The prepared perillyl acetate was first saponified yielding perillyl alcohol (the optimal method was selected), which was hydrogenated producing 4-isopropylcyclohexylmethanol. Scheme 1 shows the individual steps of the reaction.

Experimental

Chemicals

β-Pinenoxide was supplied by Aroma and used as received. Acetic anhydride, boric acid, and anhydrous magnesium sulfate were purchased from Lach-Ner. Phosphoric acid (84 %), citric acid, sodium hydroxide, methanol, and isopropyl alcohol were



Scheme 1 Reaction scheme of *cis*-4-isopropylcyclohexylmethanol synthesis from β-pinenoxide with the intermediate perillyl acetate

Table 1 Composition of catalyst SSA

Component	ZrO_2	Al_2O_3	Sulfates
Content (%)	50–60	30–40	10

Table 2 Properties of zeolite USY (CVB 720)

Ratio of Si/Al	Structure	Pore size (Å)
15	3D	7.4

purchased from Penta. Acetic acid (99 %), potassium carbonate, and anhydrous sodium carbonate were purchased from Lachema. Catalysts SSA (Table 1) and NiSAT 320 RS were supplied by Süd Chemie. Zeolite USY (CVB 720; Table 2) was purchased from Zeolyst International, montmorillonite K-10 from Aldrich, γ-alumina from ICT Prague, and *tert*-butyl methyl ether from Fluka Analytical.

Preparation of perillyl acetate

The preparation of perillyl acetate was carried out in a 2-necked flask (25 ml) equipped with a condenser. Stirring and heating was accomplished using a magnetic stirrer. In a typical experiment, 2 g (0.066 mol) of β-pinenoxide and 10 g (0.098 mol) of acetic anhydride were added to the flask and the acid catalyst was then slowly added. Then, 2 g of a homogenous catalyst was added dropwise into the reaction mixture (100 wt% to β-pinenoxide), or 0.4 g of a heterogeneous catalyst was added (20 wt% to β-pinenoxide). The reaction was carried out at the temperature of 80 °C, while the reaction progress was monitored by GC.

In the case of a heterogeneous catalysis, the catalyst had to be activated before the reaction by calcination under air at 420 °C for 1.5 h.

A subsequent rectification was carried out using a laboratory glass column (Sulzer filling) with 15 theoretical plates.

Saponification of perillyl acetate

The saponification of perillyl acetate was carried out by two methods adopted from the literature [2, 8]. Both the reactions were carried out in a flask with a condenser on a magnetic stirrer.

1. The obtained perillyl acetate and a 30 % aqueous solution of sodium hydroxide [8] were put into the flask and the heating commenced. The reaction proceeded under a mild reflux (135 °C) for 3 h. Subsequently, the top layer was separated and distilled.
2. Perillyl acetate, water, methanol, and anhydrous sodium carbonate [2] were mixed in the flask, and the reaction mixture was stirred at room temperature for 13 h. Finally, the extraction and purification of perillyl alcohol was carried out.

Hydrogenation of perillyl alcohol

Perillyl alcohol (2.4 g), nickel catalyst NiSAT 320 RS (0.24 g), and isopropyl alcohol (80 ml) were introduced into the stainless steel autoclave Parr 4843 (volume 150 ml). The following reaction conditions were used: temperature 80 °C and pressure 10 MPa. Samples were collected and analyzed using GC.

Analytical

The Agilent Technologies 6890 Network GC System gas chromatograph was used with flame ionization detection to analyze all samples. A non-polar HP-5 column was used (length 30 m, inside diameter 0.32-mm and stationary phase film thickness 0.25 µm).

The Saturn 2000 gas chromatograph combined with a mass spectrometer (GC/MS) with an ion trap and 1177 injector was used for the identification of compounds in the reaction mixture. The gas chromatograph contained a non-polar Cp-Sil 8 CB Low Bleed MS column (length 30 m and inside diameter 0.25 mm).

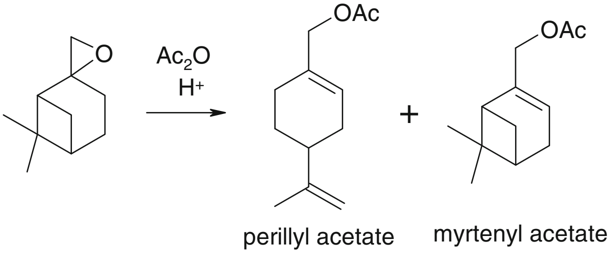
Results and discussion

Preparation of perillyl acetate

The work was dedicated to the study of perillyl acetate formed from *β*-pinenoxide. An optimal catalyst was identified, capable of opening both the rings (epoxidic and carbonic) of the initial *β*-pinenoxide. The opening of only the epoxidic ring led to the production of undesired products, in particular myrtenyl acetate (Scheme 2), whereas the desired product was perillyl acetate and its isomers.

The reaction was carried out without any solvent. Similar reactions had been carried out in *N*,*N*-dimethylformamide in previous research [11], but it was found that this solvent could initiate undesirable polymerization reactions. Dichloromethane, recommended in the previous work [3], was not tested.

The influence of temperature was studied using reaction conditions with the same reagent mass ratios as described in the experimental section (1 g of *β*-pinenoxide : 1 and 5 g of acetic anhydride : 5 g of catalyst and 1 g of acetic acid). The temperature



Scheme 2 Reaction scheme of perillyl acetate preparation

range was from room temperature to 140 °C (reflux). The reaction proceeded very quickly at both temperatures (Fig. 1 shows the course of the reaction). The yield of perillyl acetate was almost the same in all cases. The main difference in using different temperatures was in the composition of the reaction mixtures. Different isomers of perillyl acetate were observed, while the highest yield of the sum of perillyl acetate and its isomers was at 50 °C.

The optimum ratio of *β*-pinenoxide:acetic anhydride was for the reactions determined at 80 °C using acetic acid as the catalyst. The optimum ratio was found to be 1:5 *β*-pinenoxide:acetic anhydride by weight (Table 3). Using this ratio, the highest yield of perillyl acetate was obtained (78.7 %). Higher and lower amounts of acetic anhydride caused an increased formation of undesired products, in particular myrtenyl acetate in higher amounts and unidentified polymeric by-products in lower amounts.

In the following sections, the temperature of 80 °C and the ratio of *β*-pinenoxide to acetic anhydride 1:5 were used.

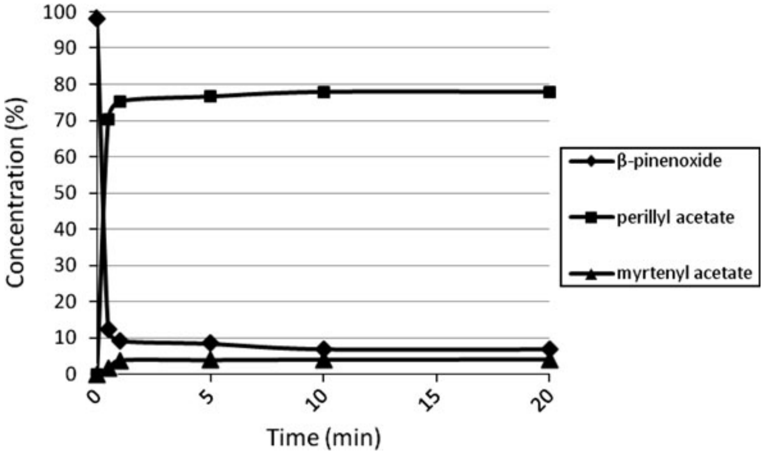


Fig. 1 Reaction course of perillyl acetate preparation (reaction conditions: 1:5:1 *β*-pinenoxide:acetic anhydride:acetic acid, 50 °C)

Table 3 Influence of the amount of acetic anhydride on the composition of the reaction mixture (reaction conditions: 2 h, 80 °C, 1:1 of *β*-pinenoxide:acetic acid)

Ratio *β*-pinenoxide: acid	Yield of perillyl acetate (%)	Yield of myrtenyl acetate (%)	Conversion of *β*-pinenoxide (%)
1:10	76.8	6.9	97.0
1:5	**78.7**	**4.0**	**94.2**
1:3	74.1	4.5	92.3
1:1	54.6	4.9	92.1

Bold type shows the highest yield

Homogenous catalysis

From inorganic acids, phosphoric acid (84 %) and boric acid were tested as homogenous catalysts, whereas acetic and citric acids were selected from organic acids.

Table 4 summarizes the results from experiments carried out with different amounts of acetic acid (99 %) used as the catalyst. The highest yield of perillyl acetate was achieved using acetic acid in 1:1 ratio to β-pinenoxide.

Two ratios of citric acid to β-pinenoxide (100 and 5 wt% acid to β-pinenoxide) were tested: 100 % conversion of β-pinenoxide was achieved using the higher ratio, but a large amount of myrtenyl acetate (33.4 %) was formed. Using the smaller ratio of the acid, the reaction yielded 58.1 % of perillyl acetate and 17.5 % of myrtenyl acetate at 91.6 % conversion of β-pinenoxide. It conspicuously demonstrated that the use of citric acid was associated with a high content of myrtenyl acetate.

H_3PO_4 and H_3BO_3 were added to the reaction mixture in 1:1 weight ratio to β-pinenoxide. In both cases, the formation of polymers was demonstrated by a change in the reaction mixture color and viscosity. Due to the more vigorous reaction using H_3PO_4 (very exothermic with an immediate color change), this acid was excluded from further experiments. H_3BO_3 was used in a mass of 20 wt% relative to β-pinenoxide. The yield of perillyl acetate was 74 % and the amount of undesired myrtenyl acetate was 5 % after 2 h at 99.8 % conversion of β-pinenoxide.

Heterogeneous catalysis

The following heterogeneous catalysts were tested for their use in the preparation of perillyl acetate: zeolite USY (CVB 720), SSA, montmorillonite K-10 [3], and γ-alumina. All these heterogeneous catalysts were added to the reaction at levels of 20 wt% relative to β-pinenoxide.

The best results were achieved using montmorillonite K-10 as the catalyst for the reaction at 80 °C using 1:5 ratio of β-pinenoxide:acetic anhydride. The reaction mixture immediately turned black after the addition of the catalyst. After 2 h, 100 % conversion of β-pinenoxide was achieved yielding 70.4 % of perillyl acetate and 4.2 % of myrtenyl acetate; 100 % conversion of β-pinenoxide was also achieved using the catalyst called SSA. The yield of perillyl acetate was only 63.9 % but there was no myrtenyl acetate in the reaction mixture. An unidentified by-product was detected in the reaction mixture at the level of 14.9 %. The same outcome was

Table 4 Influence of acetic acid amount (reaction conditions: 80 °C, β-pinenoxide:acetic anhydride 1:5)

Ratio β-pinenoxide : acid	Yield of perillyl acetate (%)	Yield of myrtenyl acetate (%)	Conversion of β-pinenoxide (%)
1:5	57.4	15.2	95.8
1:1	**78.7**	**4.0**	**94.2**
1:0.5	73.7	7.8	95.4
1:0.2	63.6	13.1	92.9

Bold type shows the highest yield

observed using zeolite USY (CVB 720). After 2 h, the yield of perillyl acetate was 55 % and myrtenyl acetate was not found in the final reaction mixture. The ring opening catalyzed by γ-alumina did not show a satisfactory performance, only a low conversion of β-pinenoxide was achieved (58.9 %) and the yield of perillyl acetate was only 33.7 %.

Table 5 summarizes the best results obtained using different catalysts.

Next, an experiment was carried out on a larger scale (2 l). The reaction conditions for perillyl acetate formation were: 1:3:1 ratio of β-pinenoxide:acetic anhydride:acetic acid at the temperature of 80 °C. The yield of perillyl acetate was 74.8 % after 2 h.

Saponification of perillyl acetate

As mentioned above, two saponification processes were adopted from the literature. The first [8] uses an aqueous solution of sodium hydroxide and the second [2] uses a methanolic solution of sodium carbonate and water. The obtained perillyl alcohol was purified by vacuum distillation at 1.2 kPa, b.p. 130 °C.

Table 6 shows the comparison of both utilized methods.

Hydrogenation of perillyl alcohol

The next step was the hydrogenation of perillyl alcohol to *cis*-4-isopropylcyclohexylmethanol (Mayol). The reaction was carried out using the nickel supported catalyst NiSAT 320 RS under the reaction conditions provided in the "Experimental" section. After 3 h, the yield of both isomers of 4-isopropylcyclohexylmethanol was 87.1 % (48.2 % of *cis*-isomer and 39 % of *trans*-isomer) at 100 % conversion of perillyl alcohol. Dihydroperillyl alcohol (7 %, equal to the sum of all isomers of dihydroperillyl alcohol) was also contained in the reaction mixture. After 6 h, the composition of the reaction mixture consisted of 94.6 % of 4-isopropylcyclohexylmethanol (54.1 % of *cis*-isomer and 40.5 % of *trans*-isomer) and 2.4 % of dihydroperillyl alcohol (Fig. 2).

Table 5 Summary of the best results obtained using homogenous and heterogeneous catalysts (reaction conditions: 80 °C, 1:5 β-pinenoxide:acetic anhydride)

Catalyst	Yield of perillyl acetate (%)	Yield of myrtenyl acetate (%)	Conversion of β-pinenoxide (%)
Acetic acid (100 wt%)	78.7	4.0	94.2
Boric acid (20 wt%)	73.5	5.1	99.8
Montmorillonite K-10 (20 wt%)	70.4	4.2	100.0
SSA (20 wt%)	63.9	0.0	100.0
Citric acid (5 wt%)	58.1	17.5	91.6
USY (CVB 720) (20 wt%)	55.0	0.0	92.9
γ-Alumina (20 wt%)	33.7	13.9	58.9

Table 6 Summary of results for both saponification methods

	The saponification using	
	30 % water solution of NaOH	Methanol solution of Na_2CO_3
Content of perillyl acetate (%)	0.0	0.7
Catalyst amount (wt% to perillyl acetate)	120	100
Yield of perillyl alcohol (%)	94.0	93.4
Yield of unknown by-products (%)	6.0	5.9
Reaction time (h)	3	13
Reaction temperature (°C)	135	85
Final processing of reaction mixture	Separation of water phase and vacuum distillation	Filtration of Na_2CO_3, elimination of methanol, extraction with *terc*-butyl methyl ether, drying with magnesium sulfate, filtration of magnesium sulfate, and vacuum distillation

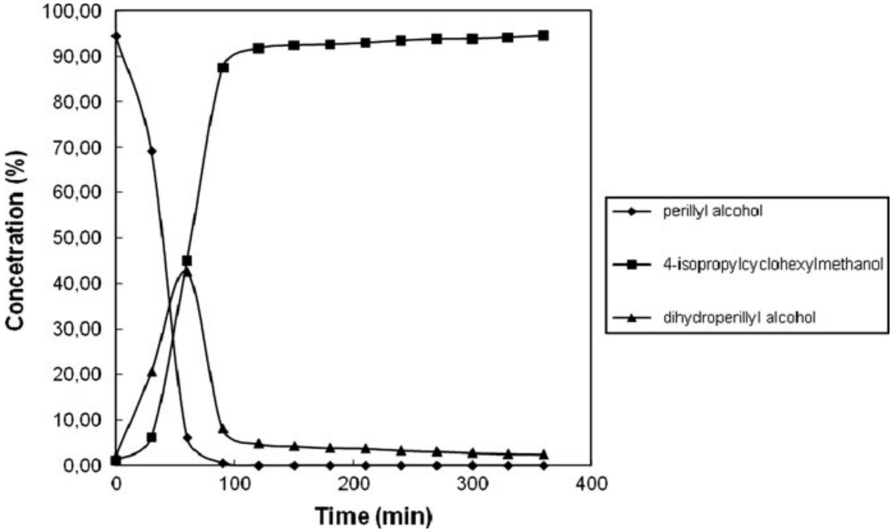
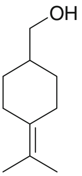
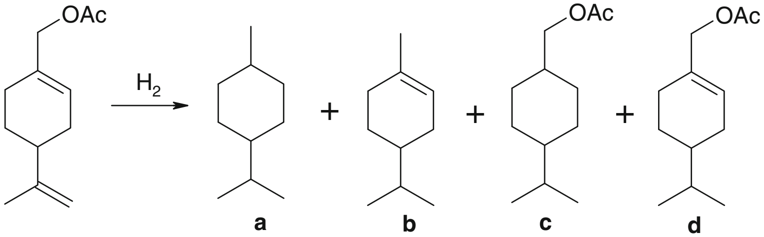


Fig. 2 Reaction course of perillyl alcohol hydrogenation (10 wt% of the catalyst, 80 °C, 10 MPa)

Various isomers of dihydroperillyl alcohol formed in the reaction mixture during the hydrogenation of perillyl alcohol. Most of these isomers were further hydrogenated. Only one of these isomers (4-(1-methylethylidene)cyclohexanemethanol, Scheme 3) remained in the reaction mixture at the level of 2.4 % after 6 h of reaction time. This isomer was resistant to hydrogenation under the selected reaction conditions.



Scheme 3 4-(1-Methylethylidene)cyclohexanemethanol



Scheme 4 Scheme of perillyl acetate hydrogenation

Hydrogenation of perillyl acetate

An alternative method for the preparation of *cis*-4-isopropylcyclohexylmethanol is the hydrogenation of perillyl acetate, followed by saponification. Hydrogenation of perillyl acetate was performed under the same conditions as the hydrogenation of perillyl alcohol (catalyst NiSAT 320 RS 10 wt%, 80 °C, 10 MPa of isopropyl alcohol). The reaction mixture analysis showed that this alternative method was not suitable for the preparation of *cis*-4-isopropylcyclohexylmethanol as high amounts of undesired products were present in the reaction mixture. Moreover, the hydrogenation itself proceeded with a lower rate. The final reaction mixture (Scheme 4) contained 37.4 % of 1-methyl-4-(propan-2-yl)cyclohexane (**a**), 1-methyl-4-(propane-2-yl)cyclohexene (**b**), 12.5 % of [4-(propan-2-yl)cyclohexen-1-yl]methyl acetate (**d**), and 32.1 % of the desired [4-(propane-2-yl)cyclohexyl]methyl acetate (**c**).

Conclusion

The preparation of perillyl acetate from β-pinenoxide was carried out followed by its conversion to perillyl alcohol and to the desired fragrant compound 4-isopropylcyclohexylmethanol (Mayol). The best results for the preparation of perillyl acetate were obtained using acetic acid (1:1 ratio related to β-pinenoxide) as the catalyst at 50 °C and an acetic anhydride ratio of 5:1 with respect to β-pinenoxide. The yield achieved of perillyl acetate was 78.7 %. Myrtenyl acetate, which was an undesired reaction product, was present in the reaction mixture at around 4 %, but the mixture was successfully distilled. After the separation steps, the yield was 67 % of perillyl acetate with its purity of 98 %.

Perillyl alcohol was prepared by saponification followed by distillation. The yield of perillyl alcohol was 94.4 at 100 % conversion of perillyl acetate**.** Finally, 4-isopropylcyclohexylmethanol was prepared. The yield of this desired fragrance compound was 47.7 % calculated on the initial β-pinenoxide.

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