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Dedicated to Professor Ionel Haiduc
on the occasion of his 65th birthday

STUDY OF ACETYLATION ON TERPINEN-4-OL. SYNTHESIS OF THE 4-TERPINENYL-ACETATE

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ABSTRACT. The reaction of terpinen-4-ol with acetic anhydride in acid or basic medium was reinvestigated. Details on the structure of the ester was established by spectroscopic methods (^{1}H-NMR and mass spectroscopy).

INTRODUCTION

Terpinen-4-ol and its acetate are natural monoterpenic compounds, used as odorants in cosmetic industry. There are many methods for separation and purification of the terpinenyl acetate[1-8], but only one method[9] concernes the synthesis of this compound and requires the treatment of terpinen-4-ol with acetic anhydride and sodium acetate in xylene by refluxing the reaction mixture for 24 hours.

Since 4-terpinenyl acetate is very important in cosmetic industry, we reinvestigated the acetylation of terpinen-4-ol.

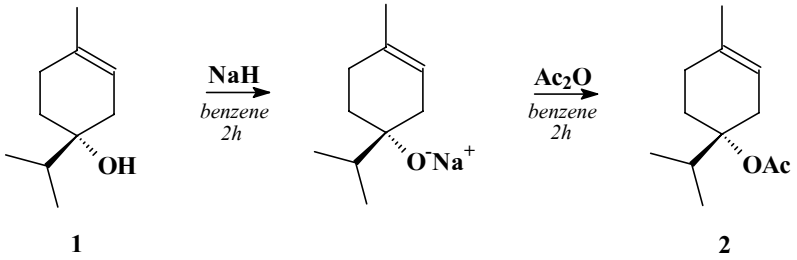
RESULTS AND DISCUSSION

We made a study concerning the transesterification reaction of terpinen-4-ol using t-butylacetate, ethylenglycol diacetate, boron triacetate as transacetylation agents. The obtained yields in ester were very low, under 30%. Because of these unsatisfactory results, we investigated the direct acetylation reaction of terpinen-4-ol with acetic anhydride in acid and basic catalysis.

Basic catalysis

The acetylation reaction in basic catalysis was performed through alcoxide intermediate. Terpinen-4-ol was treated with NaH in anh. benzene to lead the sodate intermediate. We choosed this way for obtaining the ester, because the alcoxide intermediate is better nucleofile than the alcohol in reaction with acetic anhydride.

In this reaction, the ester **2** was obtained in 61% isolated yield with 68% conversion by using equimolar amounts of starting materials (see experimental part). The low conversion and yield is explained by lower nucleophilicity of alcoxide due to the sterical hindrance of isopropyl group.



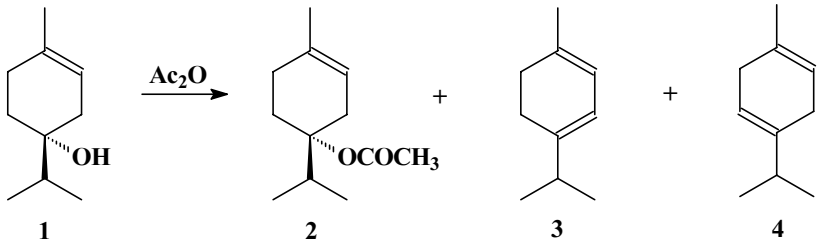
Scheme 1.

The acetylation in basic catalysis was also performed with acetic anhydride in pyridine in 65% yield (50% conversion) or acetic anhydride and sodium acetate in 52% yield (45% conversion).

Acid catalysis

The acetylation reaction with acetic anhydride in acid catalysis was performed at room temperature using equimolar amounts of starting materials, in presence of different acid catalysts: $HClO_4$, H_2SO_4, p-TsOH, H_3PO_4. The reaction was monitorized by GC-MS analysis, using a 20m siliconic capillary column. The reaction conditions and the distribution of reaction products are presented in Table 1. As shown in table 1, it was obtained smaller quantities of ester (30% yield in $HClO_4$ and 31% yield in H_2SO_4) in the presence of strong acids ($HClO_4$, H_2SO_4). In this reaction α- and γ-terpinens were obtained as major products (yields around 30% for **3** and 20% for **4**), by dehydration of terpinen-4-ol in acid catalysis (see Scheme 2). Good results were obtained using H_3PO_4 as catalyst.

The acetylation reaction in presence of H_3PO_4 was studied at different concentrations of acid and monitorized by GC-MS analysis (see table 2).



Scheme 2.

The best results were obtained at 0.1M concentration of H_3PO_4, when the concentration in ester was 72% in final reaction mixture (by gas chromatography analysis, see fig. 1).

Table 1.

Acetylation of **1** with Ac_2O in acid catalysis [a]

Acid catalyst	Alcohol unreacted (%)[b]	Products (%)[b]		
		2	**3**	**4**
$HClO_4$	1.5	30.5	30.0	20.0
H_2SO_4	4.2	31.5	32.0	18.0
p-Ts-OH	16.5	51.2	15.4	10.6
H_3PO_4	24.1	66.1	6.1	3.4

[a]All experiments were performed using equimolar amounts of starting materials at room temp. for 24 hours. Acid catalyst [c]=0.05M

[b] Analyzed by gas chromatography

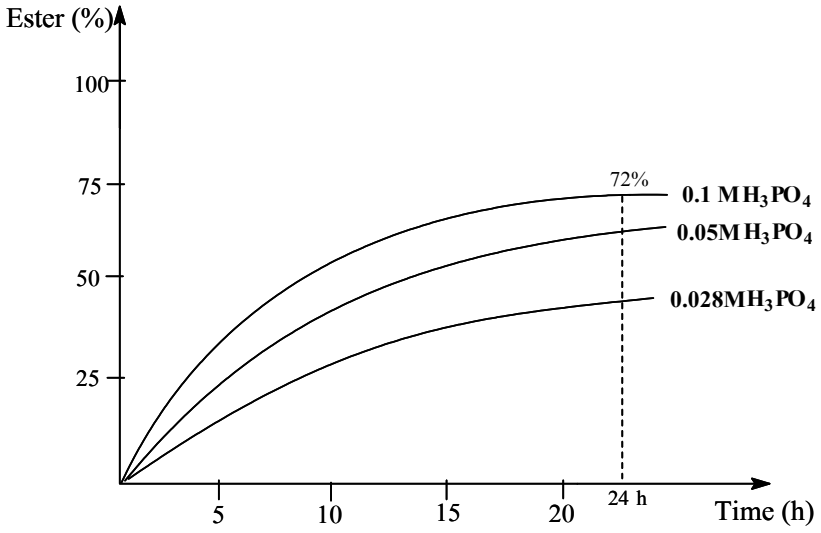


Figure 1. Variation of ester concentration at different concentrations of H_3PO_4

Terpinen-4-ol reacts in benzene at room temperature with acetic anhydride in the presence of 0.1M H_3PO_4 as catalyst to lead to acetate **2** in 90% yield and 82% conversion, analysed by gas-chromatography (see table 2).

The structure of ester **2** was confirmed by ^{1}H-NMR (see Fig. 2) and mass spectroscopy.^{1}H-NMR spectrum of compound **2** displays the caracteristic peaks for isopropyl group (position 4), methyl group (position 1) and methyl from ester group. Both methyls of isopropyl group are shown as doublet at δ=0.92 ppm (6H, J=7 Hz) and the proton from CH appears as heptet at δ=2.75 ppm (1H, J=7 Hz). The methyl group from position 1 shows as a singlet at δ=1.68 ppm and the methyl from the acetoxy group as a singlet at δ=1.98 ppm. The vinylic proton from position 2 is shown at δ=5.25 ppm as unresolved

multiplet. The chemical shifts for the equatorial and axial protons (positions 3, 5, 6) of the cyclohexane ring will be resolved by homo- and heteronuclear NMR studies.

Table 2.

Acetylation of **1** with Ac_2O in various concentrations of H_3PO_4 [a]

Time (h)	H_3PO_4 0.028M		H_3PO_4 0.05M		H_3PO_4 0.1M	
	Alcohol[b]	Ester	Alcohol	Ester	Alcohol	Ester
2	88.5	6.9	82.0	10.5	78.1	11.2
4	81.0	12.5	71.0	18.0	67.0	22.5
6	75.5	17.2	62.0	27.5	57.5	31.0
8	71.0	22.0	55.2	35.0	50.0	39.1
10	67.0	25.5	49.1	41.3	42.7	46.1
14	61.2	31.0	38.5	51.0	31.2	57.4
18	57.1	34.8	30.5	59.0	22.5	66.1
24	54.0	39.1	24.0	66.1	18.0	72.1

[a] All experiments were performed using equimolar amounts of starting materials at room temp. for 24 hours

[b] Analyzed by gas chromatography

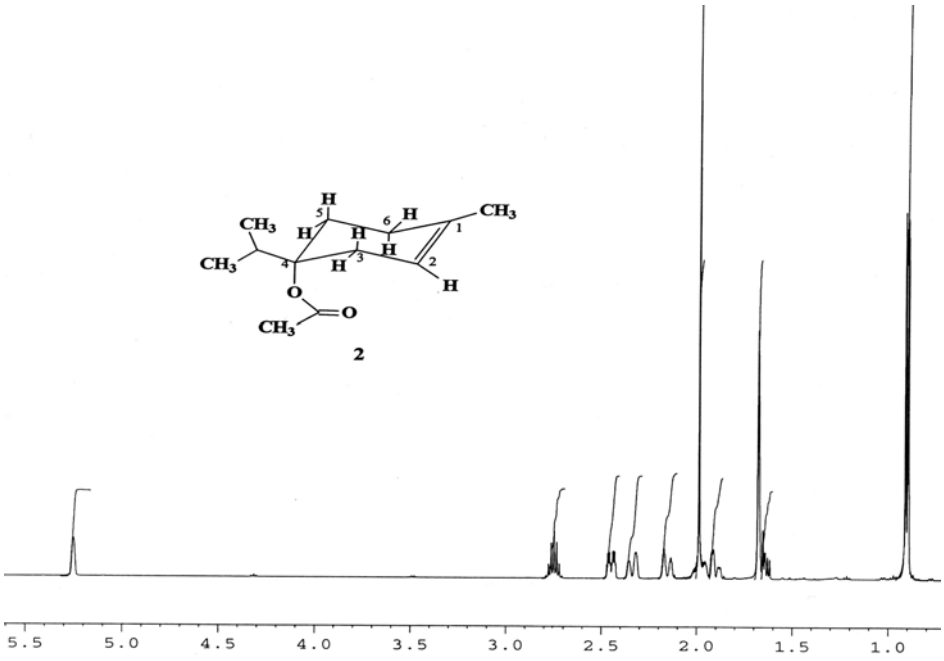


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Figure 2. ^{1}H-NMR spectrum of 4-terpinenyl-acetate

Gas chromatography-mass spectroscopy analyses confirmed the structure of terpinenyl-4-acetate. The main peak (100%) shown as m/e=93 and its formation requires the lost of acetic acid (m/e=136, 40%) and also an isopropyl group. Another important peak appears at m/e=121 (60%) due to an acetic acid and methyl group lost.

EXPERIMENTAL

Gas chromatography-mass spectroscopy (GC-MS) coupling analyses were performed on a Hewlett-Packard 5890 (GCL)-5972 (MSD) using a HP-5MS 20m x 0.25 x 0.25 μm capillary. ^{1}H-NMR spectra were recorded using $DMSOd_6$ as solvent with a 300 MHz Varian spectrometer. The reactions were also monitored by TLC using Merck plates and pethroleum ether:ethyl ether 5:1 as eluent. Terpinen-4-ol was purchased from Aldrich.

Acetylation in basic catalysis

2.4 g NaH (50%, 0.05 mole) and 100 ml benzene was refluxed for 0.5 hour and than 7.7 g terpinen-4-ol (0.05 mole) was dropwise added. The reaction mixture was refluxed for 1 hour and than acetylated by adding 5.1 ml acetic anhydride (0.05 mole) and heating under reflux for an additional 2 hours. After the reaction time was expired, the final product was washed with water, aqueous sodium carbonate solution and again with water, and than the separated organic layer was dried over Na_2SO_4 anh.. After removal of benzene under reduced pressure, it was obtained a residual oil (8 g which represents 68% ester and 32% unreacted terpinen-4-ol, by GC-analyses). A part of this residual oil (2g) was chromatographed on silicagel (80 g) using pethroleum ether : ethyl ether 5:1 as eluent and gave 1.5 g ester (61.2% yield).

Acetylation in acid catalysis

A mixture of 3.2 g (0.02 mole) terpinen-4-ol, 10 ml benzene, 3 ml of acetic anhydride and 3 ml solution (10% H_3PO_4 in acetic anhydride) was stirred at room temperature for 24 hours. The reaction mixture was then washed with water, aqueous sodium carbonate solution and again with water. The aqueous phase discarded and the benzene solution dried over anhydrous sodium carbonate. After removal of the benzene under reduced pressure, the residual oil (4g) was chromatographed on silicagel (80 g). Elution with pethroleum ether: ethyl ether (5:1) gave two main fractions, A (3.2 g, 80% isolated yield) and B (0.8 g, 20%, unreacted terpinen-4-ol).

Compound A (terpinenylacetate), pale yellow oil; b.p.=71-73^0(1.3mm), n_D^{25}=1.4623. ^{1}H-NMR, δ(ppm): CH_3 (6H, d, 0.9); CH_2 (H_{5ax}, dd, 1.6; H_{5ec}, m, 1.9); CH_3 (3H, s, 1.6); CH_3CO (3H, s, 2.0); CH_2 (H_{6ax}, dd, 1.9; H_{6ec}, dd, 2.45); CH_2 (H_{3ax}, dd, 2.25; H_{3ec}, dd, 2.35); CH(1H, hept., 2.75); CH(1H, s, 5.25). GC-MS, m/e(%): 136(40%), 121(60%), 93(100%), 43(25%).

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