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Journal of Molecular Catalysis A: Chemical 259 (2006) 99–102
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Synthesis of 1,8-cineole and 1,4-cineole by isomerization of α-terpineol catalyzed by heteropoly acid

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Received 26 April 2006; received in revised form 25 May 2006; accepted 26 May 2006
Available online 18 July 2006

Abstract

The isomerization of α-terpineol (**1**) catalyzed by heteropoly acid $H_3PW_{12}O_{40}$ (PW) in homogeneous and heterogeneous systems yields 1,8-cineole (**2**) and 1,4-cineole (**3**), both useful for flavoring and pharmaceutical applications. In the homogeneous system, **2** and **3** were obtained with 25% and 23–27% selectivity, respectively, at 50–90% α-terpineol conversion (in a nitrobenzene solution, 40 °C). In the heterogeneous system, 35% of **2** and 25% of **3** were obtained at 70–100% conversion in a cyclohexane solution at 60 °C using silica-supported PW as a solid acid catalyst, and the catalyst could be recycled. PW showed a higher catalytic activity and selectivity than conventional acid catalysts such as H_2SO_4 and Amberlyst-15.

Keywords: 1,4-Cineole; 1,8-Cineole; α-Terpineol; Heteropoly acid; Catalysis

1. Introduction

The cineoles, possessing important biological activities, are volatile, symmetrical monoterpenic cyclic ethers. These are commonly found as components of essential oils from aromatic plants [1–6]. 1,8-cineole (1,8-epoxy-*p*-menthane also known as Eucalyptol) has a characteristic fresh and camphoraceous fragrance and pungent taste. It finds various uses as aroma and pharmaceutical chemical, e.g., as a food flavoring agent, for treating symptoms of airway diseases and in aromatherapy as a skin stimulant [7–11]. Although, 1,8-cineole is traditionally more desirable and more abundant isomer, 1,4-cineole (1,4-epoxy-*p*-menthane) is also a widely distributed natural oxygenated monoterpene found in the same plant species, however usually in much lower concentrations than 1,8-cineole. Recently, the synthetic utility of 1,4-cineole has been recognized, e.g., as a valuable intermediate for the preparation of herbicides [12]. It should also be mentioned that both cineoles have important phytotoxic properties which could render them various practical applications [13].

Cineoles can be prepared synthetically by treatment of terpene fractions or isoprene with mineral acids, usually sulfuric acid [14–16]. The rearrangements of terpineols and terpin hydrate catalyzed by mineral acids is a known procedure for making cineoles, however the relevant information is scarce [17,18]. These methods use very large amounts of mineral acids per substrate and result in complex mixtures containing relatively low amounts of 1,4- and 1,8-cineole, along with other products such as menthadienes, cymenes and terpinenes. Usually, the amount of 1,8-cineole in the final mixtures does not exceed 15%, with 1,4-cineole ≤ 35%. There is a serious environmental concern about these methods due to the formation of large amount of waste. Hence, the development of a clean synthesis of cineoles is a challenging task.

Heteropoly acids (HPAs) have attracted much interest as the catalysts for clean synthesis of fine and specialty chemicals in homogeneous and especially heterogeneous systems [19–21]. Recently, HPAs have been reported as efficient catalysts for various reactions of terpenes and their derivatives such as hydration and acetoxylation [22,23], cyclization [24] and isomerization [25].

Here we report the application of heteropoly acid $H_3PW_{12}O_{40}$ (PW), the strongest HPA in the Keggin series, as homogeneous and solid acid catalysts for the isomerization of

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doi:10.1016/j.molcata.2006.05.064

α-terpineol (**1**) to 1,8-cineole (**2**) and 1,4-cineole (**3**). To our knowledge, no attempt to use HPA as well as any other solid acid catalyst for this reaction has been made so far.

2. Experimental

2.1. Chemicals

$H_3PW_{12}O_{40}$ hydrate and optically pure (*R*)-α-terpineol and were purchased from Aldrich and used as received. Nitrobenzene was purified prior to use, as described elsewhere [26].

2.2. Catalyst preparation

The silica-supported HPA catalysts, $H_3PW_{12}O_{40}/SiO_2$ (PW/SiO_2) containing 20 and 40 wt.% PW, were prepared by impregnating Aerosil 300 ($S_{BET,}$ 300 $m^2\,g^{-1}$) with an aqueous PW solution and calcined at 150 °C/0.5 Torr for 1.5 h, as described elsewhere [27]. The PW content was confirmed by ICP. The integrity of the Keggin structure of PW was proved by ^{31}P MAS NMR; the catalysts showed only a single peak at ca. −15 ppm characteristic of $H_3PW_{12}O_{40}$ [19,20]. The 20% PW/SiO_2 and 840% PW/SiO_2 catalysts had a BET surface area of 205 and 143 $m^2\,g^{-1}$ and a pore volume of 0.74 and 0.39 $cm^3\,g^{-1}$, respectively.

2.3. Isomerization of α-terpineol

The reaction was carried out in a glass reactor equipped with a magnetic stirrer at 25–60 °C. In a typical run in homogeneous systems, a solution of α-terpineol (0.15 mol/L), dodecane (0.10 mol/L, internal standard) and PW (0.25–5.0 mol% based on **1**) in a solvent (5.0 mL) was stirred under air at a specified temperature. In heterogeneous systems, the reaction was carried out similarly except the solid PW/SiO_2 catalyst (0.65–1.25 wt.%, based on the total amounts of the reaction mixture) and cyclohexane as a solvent were used. The reaction progress was followed by gas chromatography (GC) using a Shimadzu 17 instrument fitted with a Carbowax 20 M capillary column and a flame ionization detector. At appropriate time intervals, aliquots were taken and analyzed by GC. The GC mass balance was based on the substrate charged. The difference was attributed to the formation of oligomers, which were not detectable by GC. The products were identified by ^1H and ^{13}C NMR spectroscopy (Bruker DRX-400, tetramethylsilane, $CDCl_3$), GC–MS on a Hewlett-Packard MSD 5890/Series II instrument operated at 70 eV and IR (Mattson FTIR 3000/Galaxy Series). The structures of all products except 1,4-cineole were also confirmed by GC using authentic samples. 1,4-Cineole was identified in the mixtures isolated after the reaction in acetone, in which 1,4-cineole was the main product (Table 1).

3. Results and discussion

3.1. Homogeneous isomerization of α-terpineol

The acid-catalyzed transformations of α-terpineol (**1**) in the presence of PW in solution were found to yield a complex mixture of products including **2** and **3** together with limonene (**4**), α-terpinene (**5**) and γ-terpinene (**6**), as well as unidentified oligomeric products (Table 1). The reaction is likely to occur via a carbenium-ion mechanism, which may be represented by Scheme 1.

Table 1
Isomerization of α-terpineol (0.15 mol/L) catalyzed by $H_3PW_{12}O_{40}$

Run	Solvent	Catalyst (mol%)	*T* (°C)	Time (h)	Conversion (%)	Selectivity[a] (%)					
						2	**3**	**4**	**5**	**6**	Others[b]
1	$PhNO_2$	None	25	5	0	–	–	–	–	–	–
2	$PhNO_2$	0.25	25	20	37	23	18	12	9	–	38
3	$PhNO_2$	0.25	40	2	48	25	27	19	16	–	13
4	$PhNO_2$	0.25	40	5	90	25	23	13	21	6	12
5	$PhNO_2$	0.5	40	1	54	25	25	14	16	5	15
6	$PhNO_2$	0.5	40	5	97	23	15	–	24	9	29
7[c]	$PhNO_2$	0.5	40	2	47	27	30	22	20	–	1
8[c]	$PhNO_2$	0.5	40	5	100	22	15	–	27	10	26
9	$PhNO_2$	0.5	60	0.5	100	16	16	4.0	29	10	25
10[d,e]	$PhNO_2$	0.37	40	5	5						
11[d]	$PhNO_2$	30	40	0.5	100	13	16	7	25	8	31
12	MeCN	0.25	40	5	0	–	–	–	–	–	–
13	MeCN	5.0	40	5	0	–	–	–	–	–	–
14	DMF	1.0	40	5	0	–	–	–	–	–	–
15	Dioxane	1.0	40	5	14	–	21	26	–	–	53
16	Acetone	0.5	40	4	28	–	46	29	9	9	7
17	Acetone	1.0	40	6	58	–	41	26	9	9	15

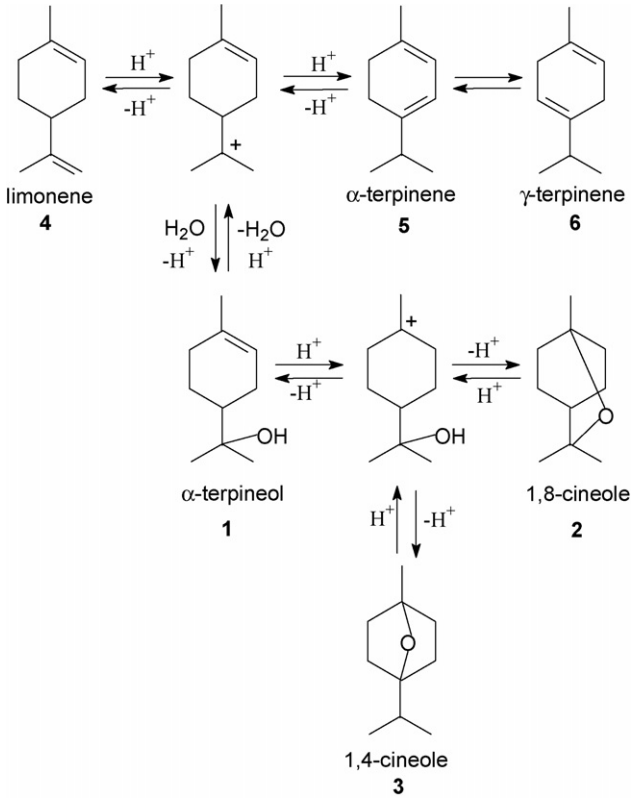
[a] Selectivity and conversion determined by GC.
[b] Mainly oligomerization products.
[c] 0.5 wt.% of H_2O added.
[d] H_2SO_4 as a catalyst.
[e] Only traces of products detected by GC.

Table 2
Isomerization of α-terpineol (0.15 mol/L) catalyzed by $H_3PW_{12}O_{40}$ (PW) in cyclohexane at 60 °C

Run	Catalyst (wt.%)	Time (h)	Conversion (%)	Selectivity[a] (%)					
				2	**3**	**4**	**5**	**6**	Others[b]
1	SiO_2 (0.65)	5	0	–	–	–	–	–	–
2	20% PW/SiO_2 (0.65)	2	100	33	24	19	18	6	–
3	20% PW/SiO_2 (1.25)	0.5	70	35	25	22	16	–	2
4[c]	20% PW/SiO_2 (0.65)	6	95	36	23	21	16	4	–
5	40% PW/SiO_2 (0.65)	1	100	33	22	17	19	7	2
6	Amberlyst-15 (0.65)	2	90	13	33	17	22	10	5

[a] Selectivity and conversion determined by GC.
[b] Mainly oligomerization products.
[c] 0.5 wt.% of H_2O added.

Solvent plays an important role in this reaction. Basic solvents, such as acetonitrile (MeCN) and dimethylformamide (DMF), completely inhibited the reaction (runs 12–14) probably due to a substantial reduction of the PW acid strength. For other solvents, the catalytic activity (α-terpineol conversion) increased with increasing the polarity (dielectric constant) of the solvent: 1,4-dioxane < acetone < nitrobenzene (runs 3, 15, 16). This result may be explained by the stabilization of carbenium-ion intermediates (Scheme 1) in the polar solvents. Interestingly, no 1,8-cineole was formed in 1,4-dioxane and acetone. In the latter solvent, the selectivity to 1,4-cineole was up to 46%, which is higher than that reported for the reaction with H_2SO_4. Nitrobenzene ($PhNO_2$) was found to be the best solvent for the reaction in homogeneous systems, which is probably due to the high polarity and cation stabilising ability of this solvent.



Scheme 1.

The isomerization of α-terpineol in $PhNO_2$ was rather slow at 25 °C (run 2). At 60 °C, the reaction rate increased dramatically to give 100% conversion in 0.5 h, although the selectivity to **2** and **3** was low (16% each, run 9). At an optimal temperature of 40 °C, **2** and **3** were obtained with 25% and 23–27% selectivity, respectively, at 50–90% α-terpineol conversion (runs 3–6). PW showed much higher catalytic activity as well as the selectivity to **2** and **3** than sulfuric acid (runs 10 and 11).

Attempting to inhibit the dehydration of α-terpineol (Scheme 1), we added some water (0.5 wt.%) to the reaction mixture. However, it did not improve the selectivity to **2** and **3**, only causing a decrease in the reaction rate (runs 7 and 8).

3.2. Heterogeneous isomerization of α-terpineol

In heterogeneous system, the isomerization of α-terpineol occurs readily in the presence of PW/SiO_2 catalyst in a cyclohexane solution (Table 2). This system is more efficient that the homogeneous one in terms of the reaction selectivity to **2** and **3**, as well as more attractive environmentally. The reaction is truly heterogeneous because PW is not soluble in cyclohexane. The catalyst can be easily separated by filtration and recycled. Thus the repeat of run 2 (Table 2) gave 95% conversion, with practically the same selectivity. No PW leaching into solution was observed (ICP analysis). The silica support showed no activity at all (run 1). With 20% PW/SiO_2, 35% selectivity to **2** and 25% to **3** was obtained at 70–100% conversion at 60 °C, with ≤2% oligomers formed (runs 2 and 3). To our knowledge, this is the best result reported so far.

Increasing the PW amount caused an increase in the reaction rate, however, without changing the selectivity (cf. runs 2 and 5). The addition of water (0.5 wt.%) to the reaction mixture (run 4) inhibited the rate of the reaction probably due to the decrease in the catalyst acid strength. But it practically did not change the selectivity of the reaction. PW/SiO_2 showed a higher catalytic activity and significantly higher selectivity to **2** compared to the acidic resin Amberlyst-15 (run 6). The latter had the selectivity similar to that of sulfuric acid, which is not unexpected.

4. Conclusions

1,8-Cineole (**2**) and 1,4-cineole (**3**), both useful compounds for flavoring and pharmaceutical applications, were synthesized

by the isomerization of α-terpineol catalyzed by heteropoly acid $H_3PW_{12}O_{40}$ in homogeneous and heterogeneous systems. In the homogeneous system, in the nitrobenzene solution, **2** and **3** were obtained with 25% and 23–27% selectivity, respectively, at 50–90% α-terpineol conversion. The reaction in the heterogeneous system was more efficient, giving 35% of **2** and 25% of **3** at 70–100% conversion in the cyclohexane solution using silica-supported PW as a solid acid catalyst, which could be recycled. $H_3PW_{12}O_{40}$ showed a higher catalytic activity and selectivity in this reaction compared to the conventional acid catalysts such as H_2SO_4 and Amberlyst-15.

Acknowledgments

Financial support from the CNPq and FAPEMIG is gratefully acknowledged. We also thank FAPEMIG for a post-doctoral scholarship for EJLL and CNPq for a doctoral scholarship for KASR.

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