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Contribution to elucidation of the mechanism of preparation of 2-isobutyl-4-methyltetrahydro-2*H*-pyran-4-ol

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Abstract The effects of catalyst type (sulfuric acid, Amberlyst 15, *p*-toluenesulfonic acid, and *p*-dodecylbenzenesulfonic acid) and of addition of water on the preparation of 2-isobutyl-4-methyltetrahydro-2*H*-pyran-4-ol by Prins cyclization were studied. It was discovered that in the absence of added water the amphiphilic character of the acid had the main effect and that organic acids were unsuitable for preparation of this compound. From the perspective of the ratio of the amount of the desired product to that of dihydropyrans, after addition of water the results obtained by use of *p*-toluenesulfonic acid (ratio 3.5, selectivity 67 %) were comparable with those obtained by use of sulfuric acid and were better than those obtained by use of Amberlyst 15 (ratio 2.3, selectivity 68 %). A detailed study of the mechanism confirmed that addition of water to the double bonds of dihydropyrans does not occur.

Keywords Prins cyclization · Water addition · Florosa · Acid catalysis

Introduction

Florosa or Florol (2-isobutyl-4-methyltetrahydro-2*H*-pyran-4-ol, Fig. 1, VI) is an important compound in the fragrance industry. It can be prepared by Prins condensation, a cyclization reaction between an aldehyde and an unsaturated alcohol [1, 2]. Prins cyclization is a very efficient reaction for production of substituted tetrahydropyranols or the dihydropyran ring. These two types of product may both be formed during the reaction and the selectivity depends on the reaction

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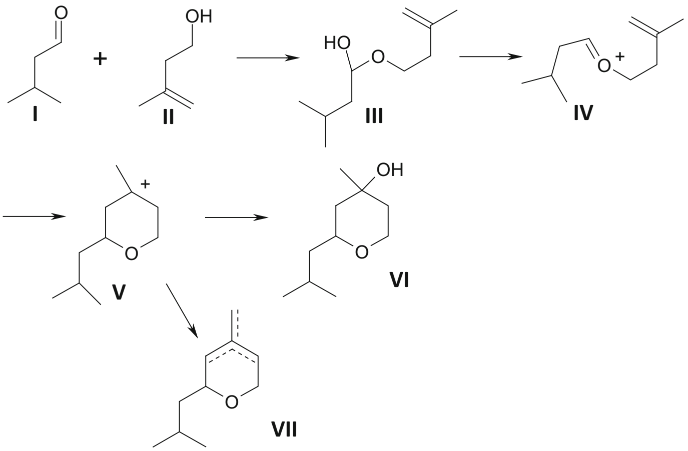

Fig. 1 Mechanism of the preparation of Florosa (**I**, isovaleraldehyde; **II**, isoprenol; **III**, hemiacetal; **IV**, carboxonium ion; **V**, carbocation; **VI**, 2-isobutyl-4-methyltetrahydro-2*H*-pyran-4-ol; **VII**, 2-isobutyl-4-methyldihydropyran)

conditions, especially the type of catalyst [3]. Lewis [4–7] or Brønsted acids (inorganic [1, 8], organic [9], or ion exchangers [10, 11]) may be used as catalysts; occasionally, heteropolyacids [12], organometallic complexes [13] or heterogeneous aluminosilicates [14] are used. The accepted mechanism [15] involves hemiacetal formation in the first step followed by cyclization to form the substituted tetrahydropyranol or dihydropyrans (Fig. 1).

It is obvious that the presence of water can affect the composition of the final reaction mixture. This fact is used when dihydropyrans are the desired product. The water formed by dehydration of the substituted tetrahydropyranol is removed, e.g., by azeotropic distillation [9] with a solvent (e.g. toluene). Selective preparation of dihydropyrans with sulfuric acid (75 % concentration) as catalyst has also been described [15]. Formation of dihydropyrans is also favored by use of high temperatures [1] compared with the temperature used for substituted tetrahydropyranol formation. Sometimes (e.g., condensation of benzaldehyde with isoprenol) it is possible to use a strong acid catalyst to selectively prepare the substituted tetrahydropyranol [1, 15]. Substituted tetrahydropyrans may also be prepared selectively by use of strong nucleophiles [2, 6, 7, 13]. If the desired product is a substituted tetrahydropyranol (in this work Florosa), the literature offers only information about changes of the reaction conditions (lower temperature) or addition of water. The latter is mentioned only for preparation of substituted tetrahydropyranols with Amberlyst 15 as a catalyst [11]; the authors recommended addition of either 10 mol% water to the reaction mixture or the amount of water that is soluble in the reaction mixture.

In this paper we report comparison of the use of different Brønsted acid catalysts for preparation of Florosa, and the effect of the addition of water to the different reaction mixtures.

Experimental

Materials

Isoprenol, isovaleraldehyde, *p*-dodecylbenzenesulfonic acid, and Amberlyst 15 (wet, 15 wt% water) were purchased from Sigma–Aldrich. Sulfuric acid and *p*-toluenesulfonic acid were purchased from Chemapol CZ. All materials were used as obtained without any purification. Water purified by osmosis (<3 mS m^{-1}) was obtained from UCT storage.

Prins condensation

In a typical reaction, equimolar amounts of isovaleraldehyde (2.15 g; 0.025 mol) and isoprenol (2.15 g; 0.025 mol) were placed in a flask equipped with a condenser. Water and the catalyst (for heterogeneous catalysts, 2.5 wt% calculated on the basis of the amount of isoprenol; for homogeneous catalysts 1 mol%; for sulfuric acid 0.5 mol%) were added to the reactants and the reaction mixture was immediately placed in a preheated (typically 70 °C) oil bath and stirred. Samples taken from the homogeneous reaction mixture were neutralized by addition of sodium carbonate, diluted with toluene, centrifuged, and analyzed by GC (Shimadzu 2010; non-polar ZB-1 column (60 m, 0.25 mm, 0.25 μm)). Mesitylene was used as internal standard.

Results and discussion

The effect of addition of water in the preparation of Florosa was tested for different catalysts with the same catalytically active group, $-SO_3H$. The catalysts were a mineral acid (sulfuric acid), organic acids (*p*-toluenesulfonic acid and dodecylbenzenesulfonic acid), and a solid catalyst with sulfonic groups as the catalytically active groups (Amberlyst 15). Catalysts were chosen on the basis of their different acidity (all results are for aqueous solutions at 25 °C: sulfuric acid $pK_a = -3$ (-1.9) [16], *p*-toluenesulfonic acid $pK_a = -2.8$ [17], *p*-dodecylbenzenesulfonic

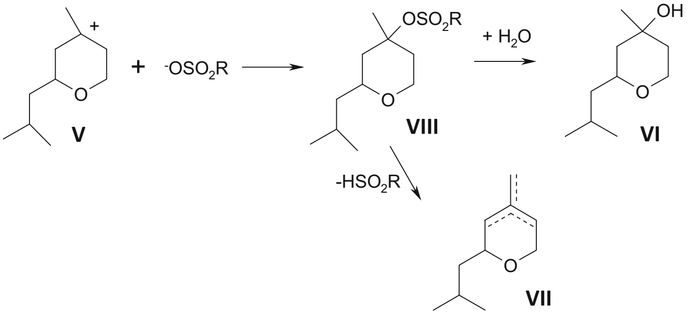

Fig. 2 Possible action of the catalyst in the reaction. R = –OH, $-C_6H_5$, $-C_{18}H_{29}$, or styrene divinylbenzene copolymer (**V**, carbocation; **VI**, 2-isobutyl-4-methyltetrahydro-2*H*-pyran-4-ol; **VII**, 2-isobutyl-4-methyldihydropyran; **VIII**, intermediate formed from carbocation and catalyst)

acid pK_a = −1.8 [18], Amberlyst 15 acidity = 4.7 mequiv H^+/g on the basis of supplier's data, pK_a < 1 [19]) and on the basis of their solubility in water and organic media. *p*-Dodecylbenzenesulfonic acid may act as a phase-transfer catalyst.

Using these catalysts, different amounts of water were added to the reaction mixture and the selectivity at 70 % conversion, the ratio of substituted tetrahydropyranol to the sum of dihydropyrans (F/DHP), and TOF were calculated. F/DHP was calculated because of the problematic separation of these two substances from the final reaction mixture and also to specify the amount of Florosa in the reaction mixture.

On the basis of the postulated mechanism [20, 21], addition of the catalysts on the basis of sulfuric acid was proposed. Formation of an intermediate (Fig. 2, **VIII**) from the conjugate base and the carbocation intermediate can be predicted. In the presence of water, a byproduct of formation of the carboxonium intermediate (Fig. 1, **IV**), hydrolysis of intermediate **VIII** and formation of substituted tetrahydropyranol occur. If water is separated from the reaction mixture by azeotropic distillation or by any other means the catalyst is regenerated by acquisition of a proton from the pyran ring and dihydropyran products are formed.

The results obtained are summarized in Table 1.

Comparison of acids without addition of water to the reaction mixture

From Table 1 (rows 1, 5, 11, 17) it is clear that the composition of the reaction products and the rate of the reaction depend on the type of catalyst. When concentrated sulfuric acid was used (no addition of water to the reaction mixture; results not included in Table 1), polymerization of isoprenol and formation of products with higher boiling points occurred. The products with higher boiling points were diacetal, formed by reaction of isovaleraldehyde with two molecules of isoprenol, and another compound with the same molecular weight (240 g/mol; the exact structure was not determined).

It should be mentioned that it is difficult to compare *p*-toluenesulfonic acid and *p*-dodecylbenzenesulfonic acid catalysts with sulfuric acid and Amberlyst 15 under water-free conditions, because the last two are always accompanied by water. This was probably one reason why the rates of the reaction and the selectivity were substantially lower when organic acids were used. The low miscibility and lowest acidity of *p*-dodecylbenzenesulfonic acid, especially, made it a poor catalyst that was unable to trap the carboxonium ion (Fig. 1, **IV**) while forming the desired substituted tetrahydropyranol.

Moreover, the organic acids used are amphiphilic in character, which may be associated with problematic transport of reactants to the active sulfonic center and with trapping of water originating during formation of the hemiacetal (Fig. 1, **III**). Both of these phenomena negatively affected reaction rate and selectivity.

As mentioned above, the greater selectivity for sulfuric acid and Amberlyst 15 was a result of two factors:

1. these compounds were not amphiphilic in character; and
2. water was always present in the reaction mixture.

Table 1 Effect of amount of water and type of catalyst on selectivity and rate of the reaction

Entry	Catalyst	Amount of water[a] (mol%)	Selectivity (%)	TOF (min^{-1})	Ratio F/DHP
1	Sulfuric acid (12 %)[c]	5	55	13.3	2.0
2	Sulfuric acid (10 %)[c]	10	52	11.8	1.9
3	Sulfuric acid (2.5 %)[c]	50	68	10.6	3.2
4	Sulfuric acid (1 %)[c]	100	63	6.1	3.2
5	*p*-Toluenesulfonic acid	0	33	3.6	0.8
6	*p*-Toluenesulfonic acid	5	59	7.9	1.1
7	*p*-Toluenesulfonic acid	10	61	7.2	2.0
8	*p*-Toluenesulfonic acid	20	61	6.8	2.6
9	*p*-Toluenesulfonic acid	50	67	5.6	3.5
10	*p*-Toluenesulfonic acid	100	62	1.2	2.4
11	*p*-Dodecylbenzenesulfonic acid	0	26	2.1	0.9
12	*p*-Dodecylbenzenesulfonic acid	5	34	5.1	1.0
13	*p*-Dodecylbenzenesulfonic acid	10	46	5.3	1.7
14	*p*-Dodecylbenzenesulfonic acid	20	56	4.8	2.5
15	*p*-Dodecylbenzenesulfonic acid	50	60	4.3	2.7
16	*p*-Dodecylbenzenesulfonic acid	100	49	0.4	1.7
17	Amberlyst 15	0	62	2.3×10^{-3}[b]	1.6
18	Amberlyst 15	5	67	2.3×10^{-3}[b]	2.2
19	Amberlyst 15	10	68	2.4×10^{-3}[b]	2.3
20	Amberlyst 15	20	63	1.8×10^{-3}[b]	2.3
21	Amberlyst 15	50	61	8.3×10^{-4}[b]	1.6
22	Amberlyst 15	100	56	3.3×10^{-4}[b]	1.3

[a] Calculated on total amount of reaction mixture

[b] Rate of reaction using solid catalyst calculated in mmol/mg min

[c] Concentration of sulfuric acid in water

Lower selectivity when sulfuric acid, rather than Amberlyst, was used was explained by the formation of products with higher boiling points (especially diacetal) and almost no formation of this type of undesirable product when solid Amberlyst 15 was used. The F/DHP ratio was higher when sulfuric acid was used, however, probably because of the greater amount of water in the reaction mixture.

Effect of addition of water

Severe phase-transfer problems were apparent when Amberlyst 15 was used. Decreases in the rate of reaction and selectivity were observed (Table 1, rows 17–22) when the amount of water was increased from 10 mol%. This was because of coating of the catalyst surface with water and by problematic transfer of organic compounds to the active centers on the surface. Agglomeration of the catalyst in the aqueous phase of the reaction mixture was also apparent when the amount of water added exceeded 10 mol%. The decrease of selectivity when this catalyst was used corresponds to the decrease of the F/DHP ratio. In comparison with the maximum F/DHP values obtained for the other catalysts, that for Amberlyst 15 (2.3) was lowest (3.5 was observed for *p*-toluenesulfonic acid and 3.2 for sulfuric acid).

The amount of sulfuric acid, calculated on the basis of the amounts of reactants, was the same for all the experiments, only the amount of water was different (and therefore, also, the concentration of the acid, as is apparent from Table 1, rows 1–4). The decrease in the rate of the reaction in this instance was caused by dilution of the acid by the water and by transfer of the sulfuric acid in the water to the organic phase. The selectivity for substituted tetrahydropyranol increased as the amount of water was increased to 50 mol%. When 100 mol% water was used a slight decrease of selectivity was observed, because of increased formation of products with higher boiling points.

After addition of water to reaction mixtures in which organic acids were used as catalysts, substantial increases of the rate of the reaction and selectivity were observed (increases from 33 and 26 % to 67 and 60 % for *p*-toluenesulfonic acid and *p*-dodecylbenzenesulfonic acid, respectively). When *p*-toluenesulfonic acid was used (Table 1, rows 5–10) the highest rate of the reaction was observed for use of 5 mol% water. The same trend as when sulfuric acid was used was observed with increasing amounts of water in the reaction mixture, i.e., a decrease in the rate of the reaction. The difference between sulfuric and *p*-toluenesulfonic acid was probably because of the different solubility of these compounds in water and the amphiphilic character of the latter, because their acidity was comparable. Selectivity for the desired compound increased on addition of water, and the highest value was observed when 50 mol% water was used. After addition of 100 mol% water a decrease in selectivity was observed, because of the decrease of the F/DHP ratio.

When *p*-dodecylbenzenesulfonic acid was used, one interesting observation was that addition of water gradually increased selectivity but, again, only up to 50 mol%. It is possible that at this concentration water makes the mixture homogeneous and that this catalyst also partially serves as a phase-transfer catalyst. When this catalyst was used, the highest rate of the reaction was observed after addition of 10 mol% of water. The rate of the reaction decreased with increasing amounts of water, and when 100 mol% of water was added the rate of the reaction was even lower than when no water was added. Addition of 100 mol% water had a detrimental effect on both the rate of the reaction and on selectivity, possibly because micelle formation made the acid head group unavailable for catalysis. The different rates of reaction for *p*-toluenesulfonic acid and *p*-dodecylbenzenesulfonic acid were because of the lower acidity and significant amphiphilic character of the latter.

In the presence of water the catalysts may be ordered according to decreasing selectivity as follows sulfuric acid ≈ Amberlyst 15 ≈ *p*-toluenesulfonic acid > *p*-dodecylbenzenesulfonic acid and according to F/DHP ratio as follows *p*-toluenesulfonic acid ≈ sulfuric acid > *p*-dodecylbenzenesulfonic acid > Amberlyst 15. This means that use of Amberlyst 15 resulted in the smallest amount of products with higher boiling points. The largest amount of this type of byproduct was obtained when sulfuric acid was used.

To explain the positive shift of the yield of the desired substituted tetrahydropyranol and, in the presence of water, suppression of dehydration of substituted tetrahydropyranol to undesired dihydropyrans, it can be assumed the water served as a hydrolyzing agent (Fig. 2, **VIII**).

Calculation of rate constants

The purpose of the work discussed in this paper was to discover how the presence of water affected the composition of the products of the reaction. Calculation of power-law kinetics by use of the software ERA 2.0 led to a possible reaction mechanism (Fig. 3).

Although the intermediate formed by the catalyst (compound **7** in Fig. 3) was not detected in the reaction mixture, the substituted tetrahydropyranol and dihydropyrans are formed in this step, and undesired products with a higher boiling point (**6**, Fig. 3) are probably formed directly from the hemiacetal (**3**). Because the intermediate was not observed in the reaction mixture, calculation of rate constants for formation of substituted tetrahydropyranol and of dihydropyrans was not possible. The "selectivity" s_3 of the reaction rate was introduced into the calculation and, hence, the rates of formation of compounds (**4**) and (**5**) were determined as follows (Eqs. 1 and 2):

$$r_3^* = k_3^* \times c_3 = k_2 \times s_3 \times c_3 \tag{1}$$

$$r_4^* = k_4^* \times c_3 = k_2 \times (1 - s_3) \times c_3 \tag{2}$$

where r_3* and r_4* and k_3* and k_4* are the apparent reaction rates and rate constants for formation of compounds **4** and **5**, respectively, k_2 is the rate constant for formation of intermediate **7**, s_3 is the selectivity for formation of product **4**, and c_3 is the concentration of the intermediate hemiacetal **3**. Formation of products with higher boiling points was determined by the concentration of hemiacetal (**3**) and by the concentration of isovaleraldehyde, because during the course of the reaction isovaleraldehyde was consumed quickly and the amount of acetal was lower than the amount of the unidentified product of molar weight of 240 g/mol.

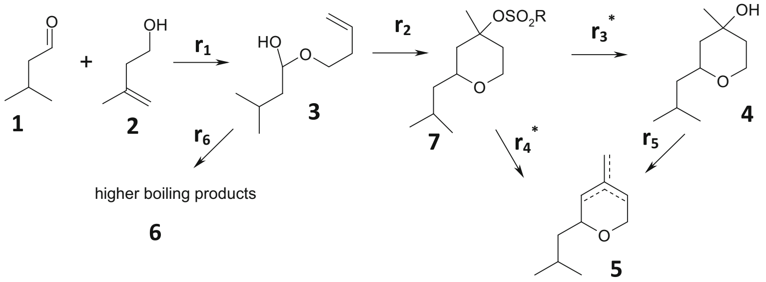

Fig. 3 Suggested mechanism for calculation of rate constants

Table 2 Examples of calculated rate constants (power-law kinetics)

Entry	Acid/amount of water (mol%)	k_1 (mmol^{-1} min^{-1})	k_2 (min^{-1})	s_3 (–)	$k_5 \times 10^{-4}$ (min^{-1})	k_6 (mmol^{-1} min^{-1})
1	pTS/0	0.93	0.113	0.385	0	10.3
2	pTS/5	5.33	0.829	0.588	1	9.2
3	pTS/10	3.17	0.442	0.632	1	4.12
4	pTS/50	1.28	0.162	0.739	0	2.12
5	pTS/100	0.76	0.095	0.605	0	4.03
6	pDBS/50	1.41	0.15	0.712	0	1.48
7	Amb/0	3.61	0.30	0.602	8.4	0
8	Sulfuric/10	3.32	0.858	0.636	3.2	10.3
9	Sulfuric/50	2.77	1.89	0.727	2.6	2.2
10	Sulfuric/100	0.45	0.04	0.769	0	0.36

From the calculations (Table 2) it is obvious for homogeneous catalysts that with increasing amounts of water the overall rate of the reaction decreases (rows 1–5 and 8–10). The rate of dehydration described by r_5 was almost 0, except for Amberlyst 15 as catalyst without addition of water and for sulfuric acid, with which dehydration was expected (rows 7 and 8). The value of s_3 monitoring the rate of production of substituted tetrahydropyranol also increased with increasing amount of water up to 100 % mol excess water, when dilution of the acid had an effect. The rate of formation of products with higher boiling points also decreased with increasing amount of water.

Conclusions

Preparation of 2-isobutyl-4-methyltetrahydro-2*H*-pyran-4-ol, also called Florosa, was discussed. Acid-catalyzed Prins condensation of isoprenol and isovaleraldehyde was used for the reaction. The study was focused especially on the effect of catalyst type and of addition of water to the reaction mixture. It was discovered that the character of the catalyst, with an active sulfuric or sulfonic acid group, has a significant effect on the composition of the reaction mixture and it is difficult to compare sulfuric acid and Amberlyst 15 with *p*-toluenesulfonic and *p*-dodecylbenzenesulfonic acids because the first two are always accompanied by water. Addition of water also had a significant effect, which was most apparent for the catalyst with amphiphilic character—*p*-dodecylbenzenesulfonic acid. With this catalyst and addition of 100 mol% water, possible micelle formation made the acid head group unavailable for catalysis.

The highest selectivity (68 %) was obtained by use of Amberlyst 15 as catalyst with addition of 5–10 mol% water, or by use of sulfuric acid (2.5 % concentration in water) and *p*-toluenesulfonic acid as catalysts, both with addition of 50 mol% water. The highest F/DHP ratio (3.5) for the desired substituted tetrahydropyranol was obtained by use of *p*-toluenesulfonic acid as catalyst with addition of 50 mol%

water. The low F/DHP ratio (2.3) at comparable selectivity for Amberlyst 15 can be explained by the presence of a small amount of products with higher boiling points compared with use of the other catalysts. It was confirmed that water has a positive effect on the reaction, especially when homogeneous catalysis is used, but the water does not interact with dihydropyrans during the formation of Florosa.

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