

New Methods

The Synthesis of Ionones

Utilizing the sole solid NaOH as the catalyst for the condensation of citral with acetone

Libor Cervený, Antonín Marhoul and Lenka Zoubková, Institute of Chemical Technology

Ionones have a broad spectrum of utilization in the flavor and fragrance industry because of their characteristic violet fragrance. Most often, the synthesis of ionones consists of two steps. First is the synthesis of pseudoionone, which is most often prepared by aldol condensation of citral with acetone in the presence of a basic catalyst. The second step is cyclization of the acquired pseudoionone in the presence of an acidic catalyst, which produces a mixture of ionones.

The majority of works utilize alkaline hydroxides for the condensation and inorganic and organic acids for the cyclization. The ratio of the acquired α - and β -isomers depends on the selection of catalyst, reaction temperature and cyclization time.

Theoretical

The ionone synthesis consists of two steps. First, pseudoionone is prepared by the aldol condensation of citral with acetone in the presence of a basic catalyst (F-1). In the second step, pseudoionone is cyclized in an acidic environment to α -ionone, β -ionone and γ -ionone, respectively (F-2). These isomers differ in the position of their double bond.

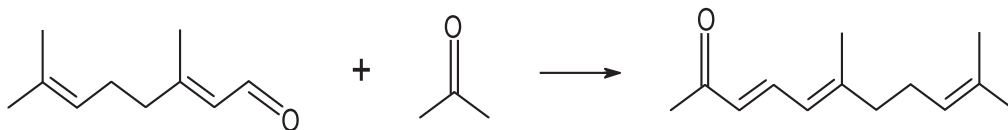
Pseudoionone is commonly prepared by condensation of citral with acetone.¹⁻⁶ The procedure restrictively leads to two demanded isomers of pseudoionone, i.e. two 3-*trans*,5-*cis* and 3-*trans*,5-*trans* isomers. The condensation of citral with acetone is most often carried out in the presence of sodium, potassium or barium (II) hydroxide. Absolute alcohol or water with an excess of acetone is a suitable environment. Sodium methoxide, ethoxide, phenoxide, quaternary ammonium bases and other basic substances can catalyze

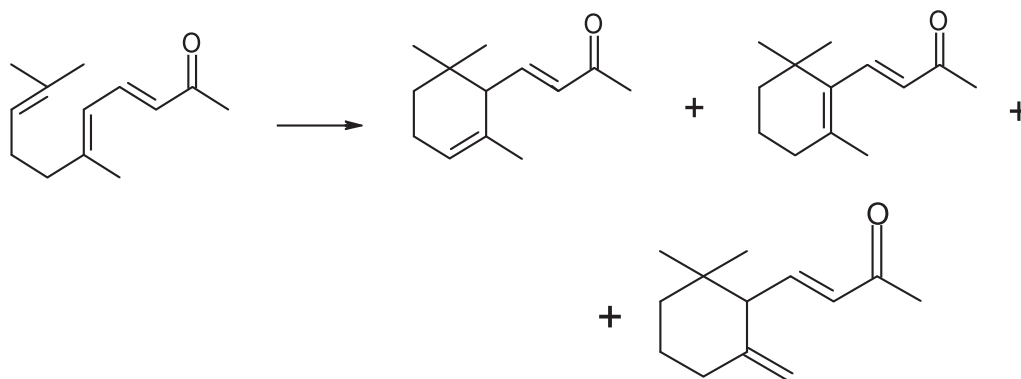
the reaction well. The range of yields of pseudoionone is 70-80 percent. It was demonstrated that the condensation can be also catalyzed using ion-exchangers that guarantee pseudoionone production in high yields with a low quantity of waste substances in a period of time shorter than 6 h.^{5,7} Divinylstyrene copolymers with the active groups of $-\text{CH}_2-\text{N}(\text{CH}_3)_2$ or $-\text{CH}_2-\text{N}^+(\text{CH}_3)_3$ activated by water solution of sodium hydroxide, Wofatit SBW and others were proved as suitable ion-exchangers.

The pseudoionone cyclization is carried out in the presence of very acidic catalysts (most often mineral acids), and commonly a product is acquired that contains a mixture of α - and β -, and γ -ionone, respectively. It was found that β -ionone is produced by cyclization carried out by concentrated sulfuric acid; a mixture of α - and β -ionone is produced by a cyclization carried out using a very diluted sulfuric acid (5 percent), and primarily, α -ionone is produced by cyclization carried out with 85 percent concentrated phosphoric acid or by use of other weak acids.² The ratio of the product isomers and their interrelationship depends on a catalyst type, its quantity and concentration, reaction

Step one of ionone synthesis

F-1





time, and temperature. Additionally, the isomer ratio is dependent on the starting ratio of isomers of pseudoionone (*trans,cis* or *trans,trans* pseudoionone).⁴

The methods of pseudoionone cyclization to β -ionone utilize a concentrated sulfuric acid in a three to six times weight excess related to pseudoionone. The process is carried out under a low-temperature, short period of time and in low-boil-

ing-point inert solvents. BF_3 and 85 percent solution of H_3PO_4 turned out to be the most appropriate catalysts for the cyclization of pseudoionone to α -ionone. Phosphoric acid is used in a quantity of 3-15 percent wt; the cyclization is carried out in chloroform, hexane or dimethylformamide. An alternative method is the cyclization in the presence of perchloric acid. Utilization of fluorsulfuric acid seems to be more advantageous, due to being substantially more reactive.⁹

The authors assumed that the usage of an acid excess in the cyclization of pseudoionone is determined by the two following circumstances.¹⁰ First, the acid excess minimizes the process of cationic polymerization of the starting pseudoionone. Second, in the case of cyclization of compounds that have more functional groups in their molecule than the double bond $\text{C}=\text{C}$ (e.g. $\text{C}=\text{O}$, etc.), the equimolar amount of acid is necessary for the protonation of these groups, whereas at lower temperatures, complexes, whose cyclization starts only in the presence of a free acid, are produced. From these assumptions, low temperature dependencies of the cationic polymerization rate and the rapid decrease of protonated complexes at higher temperatures, the authors concluded to proceed with the pseudoionone cyclization catalyzed by a small quantity of the acid under sufficiently high reaction temperatures (100°C and more).

During cyclization of pseudoionone under the presence of a small catalyst quantity, a solvent selection plays an important role. Although the reaction proceeds with satisfactory yield even in its absence, the best results are achieved when hydrocarbonic solvents or their halogen derivatives are used.

It was found that cyclization of pseudoionone first produces α -ionone, which rearranges to a thermodynamically more stable β -ionone due to the effect of an acidic catalyst.¹¹ Isomerization of α -ionone to β -ionone proceeds rapidly, with total conversion only under increased temperatures. Phosphoric acid and 60 percent sulfuric acid are not capable of inducing this isomerization, even at 40°C.

Preparation procedures that focused primarily on the preparation of α -ionone and β -ionone were found in the literature.^{2,12-14}

Experimental

The compounds used in the experiment are listed below; the catalysts used are listed in T-1.

Citral — 98 percent — Slovakofarma — distilled (103°-105°C/1.47 kPa)

Acetone — p.a. — Lachema Brno

Toluene, Cyclohexane — p.a. — Penta Chrudim

Working procedures: a) 722 g of acetone and 27 g of 41 percent aqueous solution of sodium hydroxide were introduced to a 2000 mL flask. Then 500 g of citral was added to the mixture under stirring at laboratory temperature. The mixture was heated using water bath and stirred for a period of 1.5 h at 40°C. The water layer was separated, and the organic layer neutralized by 1 percent hydrochloric acid, washed by distilled water and dried by anhydrous sodium sulfate. Acetone residues were replaced, and the product was purified by rectification. The yield of pseudoionone (b.p. 119°-121°C/0.4 kPa) was 63.1 percent.

b) 2 g of citral, 0.2 g of tetradecane (internal standard) and 7.6 g of acetone (10x excess) were introduced into a 25-mL reactor. The mixture temperature was adjusted to the required 56°C, and then 0.5 g of a hydrotalcite catalyst was added. Samples for a chromatographic analysis had been withdrawn during the course of the reaction.

c) 2 g of pseudoionone, 0.2 g of tetradecane (internal standard) and 8 mL of toluene were introduced into a 25-mL reactor. The mixture temperature was adjusted to the required 80°C, and then 0.2 mol of 85 percent H_3PO_4 was added. Samples for a chromatographic analysis were withdrawn during the course of the reaction.

Analytical methods: The analyses were operated on the gas chromatograph GC-17A Shimadzu with flame ionization detector. A capillary column (30 m x 0.32 mm) — coated with Carbowax 20M, film thickness of 0.25 μ m — was used for the identification. The analyses of the reaction mixtures were carried out isothermally at 185°C.

Pseudoionone Preparation Using Homogeneous Catalysts

Effect of reaction environment: Aldol condensation of citral was catalyzed using the sole NaOH, 40 percent aqueous solution or methanolic solution of NaOH with the molar ratio of citral:acetone 1:10. The measured data were evaluated as the time dependencies of the pseudoionone concentration (F-3) in various environments at the temperature of 56°C and with the same catalyst quantity (0.04 g NaOH per 0.013 mol of citral). It is apparent from F-3 that the reaction catalyzed purely by the solid NaOH had the highest starting reaction rate. In the reaction carried out in the methanol solution of NaOH, such content of pseudoionone in the reaction mixture was not achieved compared to the case of the reactions catalyzed by the sole NaOH or the aqueous solution of NaOH. Additionally, in the former case, a quantity decrease of the product by consecutive reactions was observed.

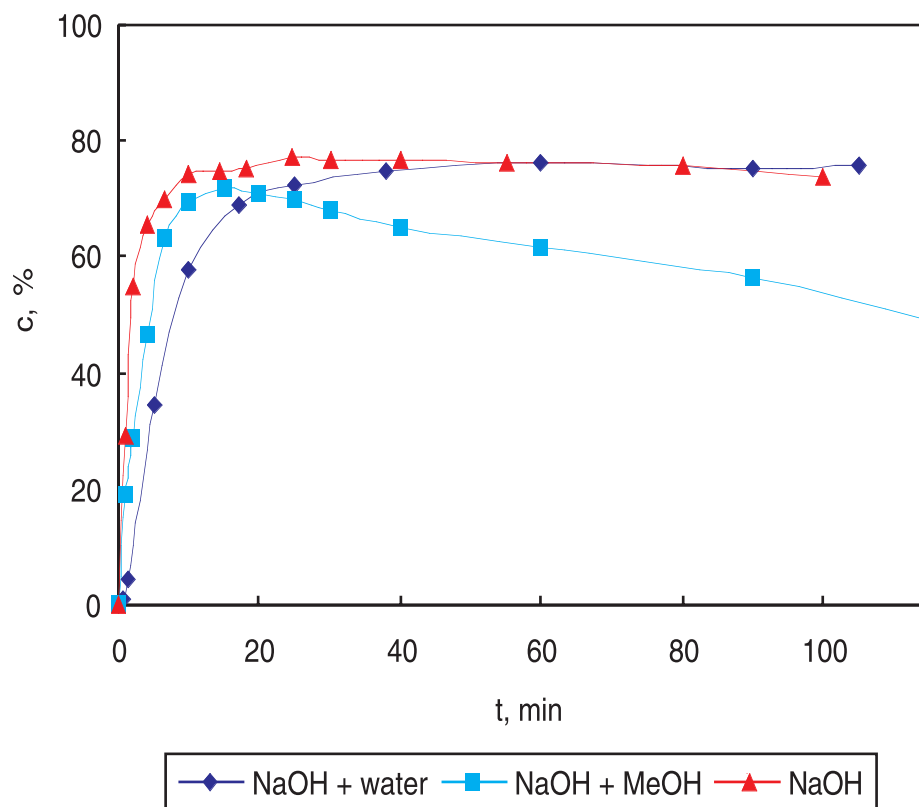
Effect of the reactants molar ratio:

In the literature, a broad spectra of molar ratios of citral:acetone was described. The experiments were performed with the molar ratios 1:3.8, 1:5, 1:10, 1:12, 1:15 and 1:20, all catalyzed by 0.04 g of NaOH under the temperature of 56°C. The reaction

Catalysts used during experiments

T-1

Catalyst	Manufacturer	Modification
NaOH	Lachema Brno	
Hydrotalcite Mg:Al = 4:1	Department of Chemistry of Solid Substances, ICT	Calcined 7 h at 530°C
Hydrotalcite Mg:Al = 2:1	Department of Chemistry of Solid Substances, ICT	Calcined 5 h at 450°C
Hydrotalcite Mg:Al = 3:1	Department of Chemistry of Solid Substances, ICT	Calcined 7 h at 530°C
Hydrotalcite Mg:Al = 5:1	Department of Chemistry of Solid Substances, ICT	Calcined 7 h at 530°C
MgO	Department of Chemistry of Solid Substances, ICT	Calcined 7 h at 530°C
H_3PO_4	Lachema Brno	
H_3PO_4 on kieselguhr	Chemopetrol Litvínov	



c = concentration of produced pseudoionone related to its theoretic concentration, expressed in percentages; t = time (min)

product quantity increased with a growing amount of acetone in the reaction mixture. When a lower molar ratio of citral:acetone was applied, auto-condensation reactions of citral conspicuously increased their action, which lead to a decreased amount of the acquired product. Having applied a higher molar ratio, a decrease of the product quantity by consecutive reactions was observed after reaching the maximum content of pseudoionone in the reaction mixture. Additionally, it was found that the starting condensation rate decreases with an increasing quantity of acetone. T-2 lists the starting reaction rate and pseudoionone content.

Temperature effect: Condensations catalyzed by NaOH were carried out at the temperature of 20°C, 40°C and 56°C; the catalyst amount was 0.04 g of NaOH, and the molar ratio of citral:acetone 1:10. T-3 gives the starting reaction rates.

The activation energy ($E^* = 23.6$ kJ/mol) was determined from the characteristics of the reaction courses carried out at

different temperatures.

The produced pseudoionone was analyzed using mass spectrometry, which showed that the first isomer was 3-*trans*-5-*cis*-pseudoionone (E,Z) and the second 3-*trans*-5-*trans*-pseudoionone (E,E).

Pseudoionone Preparation Using Heterogeneous Catalysts

Experiments with heterogeneous catalysts, hydrotalcites and MgO were carried out. The effect of reaction conditions on the reaction course and the yield of the produced pseudoionone were studied with these catalysts.

The effect of the catalyst amount, i.e. hydrotalcite (M72-the ratio of Mg:Al = 4:1), was studied in the condensation of citral with acetone at 56°C, and the molar ratio of citral:acetone 1:10. The time dependencies of the reaction courses were measured with catalyst amounts of 0.3 g, 0.5 g and 0.7 g to 0.013 mol of citral (F-4). The acquired data demonstrated that the condensation rate increased with an increasing amount of the catalyst. When 0.3 g of the catalyst was used, the reaction was too slow. Using 0.5 g and 0.7 g of the catalyst, the changes in the reaction rates were not as significant

**Starting reaction rate and pseudoionone content
(in the time 10 min)**

T-2

Mol ratio of citral:acetone	r [mol/l/min]	Pseudoionone content [percent]
1:3.8	0.45	54.0
1:5	0.40	57.2
1:10	0.31	74.1
1:12	0.18	74.3
1:15	0.13	75.7
1:20	0.11	84.3

Starting reaction rates

T-3

Temperature [°C]	r [mol/l/min]
20	0.10
40	0.19
56	0.31

Starting reaction rates at various temperatures

T-4

Temperature [°C]	r [mmol/min/g _{cat}]
40	0.20
56	0.38
66	0.46

compared to the previous case.

Effect of the temperature: The reactions were carried out at 40°C, 56°C and 66°C. The reaction at 66°C, which is 10°C higher than the boiling point of acetone, was carried out in an enclosed vessel. The reaction was catalyzed using 0.5 g of hydrotalcite per 0.013 mol of citral, with the molar ratio of citral:acetone 1:10. A decrease of the temperature under the boiling point of acetone (56°C) significantly altered the quantity of the acquired product. A temperature increase above the boiling point of acetone caused a minor effect on the acquired quantity of pseudoionone. An increase of the temperature naturally led to an increase of the reaction rate. T-4 lists the starting reaction rates at various temperatures.

The activation energy of the condensation ($E^* = 30.6$ kJ/mol) was determined from the characteristics of the reaction courses carried out at different temperatures.

Effect of reactants'

molar ratio: Experiments with citral:acetone molar ratios of 1:5, 1:10 and 1:20 were carried out at 56°C and catalyzed using 0.5 g of hydrotalcite per 0.013 mol of citral. F-5 conspicuously shows that the quantity of the acquired pseudoionone increased with a growing amount of acetone in the reaction mixture. The starting reaction rates were relatively similar in relation to utilization of dissimilar molar ratios of citral:acetone, i.e. approximately 0.38 mmol/min/g_{cat}.

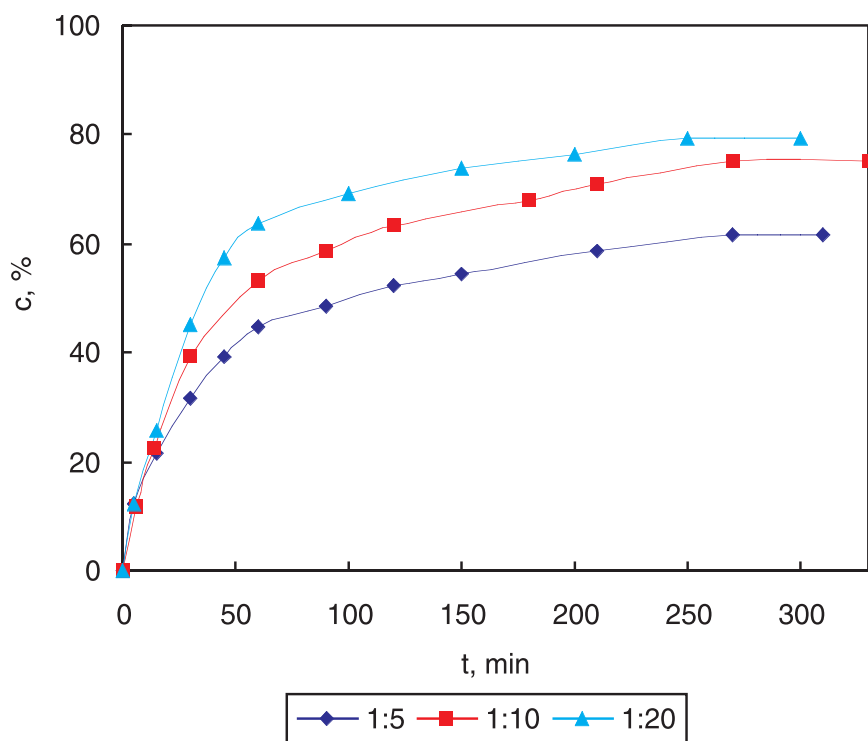
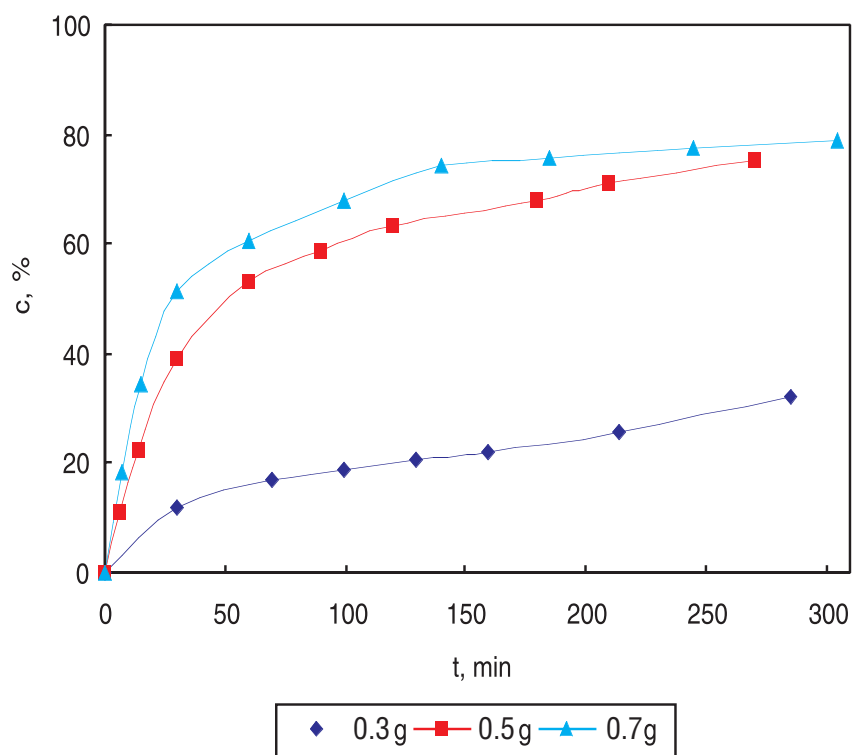
Mg:Al ratio effect:

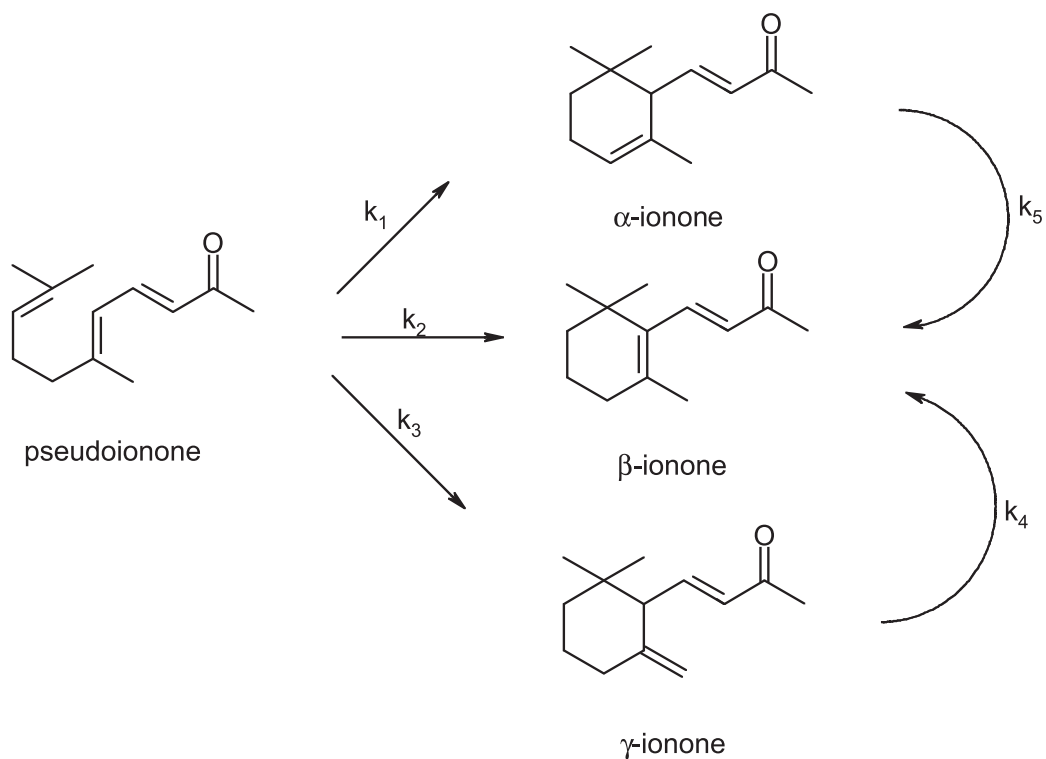
Hydrotalcites exist in various compositions, which differ in their ratio of Mg:Al. Comparative studies with Mg:Al ratios 2:1, 3:1, 4:1 and 5:1 and the sole MgO were carried out at 56°C, and catalyzed using 0.3 g of the catalyst per 0.013 mol of citral with 10 mol excess of acetone. The highest content of the required product was determined in the reaction

catalyzed by hydrotalcite with the ratio of Mg:Al 3:1. A further increase of the ratio of Mg:Al led to a decrease of the pseudoionone content. The temperature effect and the duration of calcination can explain the decrease of the pseudoionone content. The hydrotalcite used was already calcined prior to the utilization in this experiment, though at a lower temperature (450°C) and only for 5 h. The reaction catalyzed by MgO exhibited the highest starting rate, though it produced the lowest pseudoionone content.

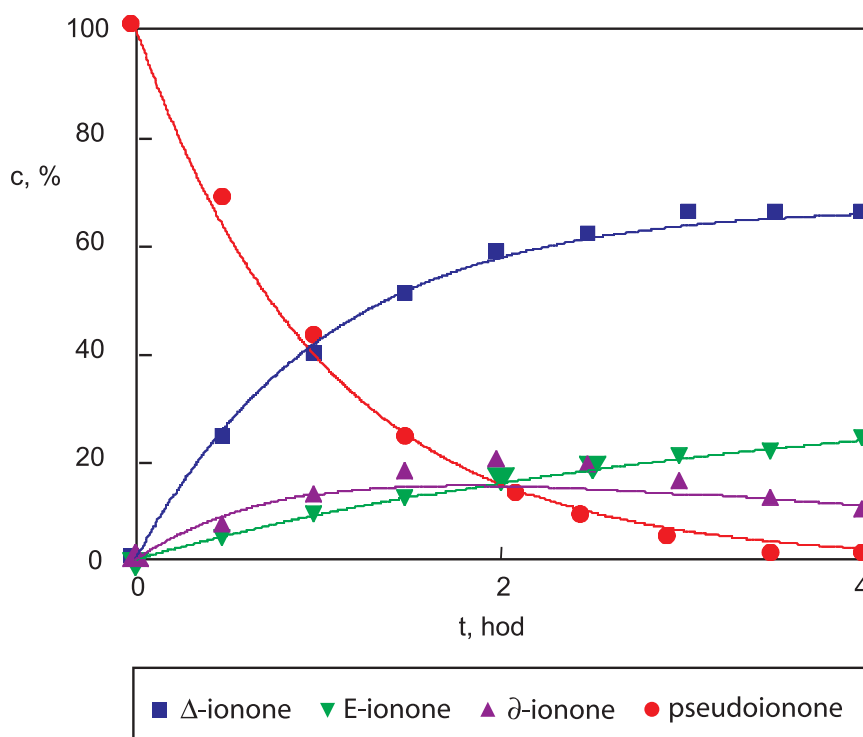
Pseudoionone Cyclization Catalyzed by H₃PO₄

Cyclization catalyzed by 0.2 mol of 85 percent solution of H₃PO₄ per 1 mol of pseudoionone with 7 mol-excess of toluene as the solvent was studied. The only reference found in the literature was 2 h of the reaction time.¹⁰ Having prolonged the reaction time, it was found that the authors presented a period of time in which the highest quantity of all isomers were acquired, especially γ -ionone, which rearranges to a thermodynamically more stable β -ionone by a further action of an acidic catalyst. Based on this finding, a model for pseudoionone cyclization to individual isomers was formulated (F-6).





Effect of cyclization of pseudoionone catalyzed by H_3PO_4
(individual points = measured values; curves = calculated model)



The acquired data were processed as the time dependence of concentration of ionones and are shown in F-7. These data were analyzed using the program ERA 2.0, which is a suitable assessment tool for experimental data and identification of mathematical models. During this analysis, it was assumed that all the reactions were of the first order, and k_5 equaled 0 as a result of the transformation of α -ionone to β -ionone, having been suppressed by the utilization of a weak acid as the catalyst.

Using this model, the following reaction rate constants particular to each individual isomer were calculated:

$$\begin{aligned}k_1 &= 0.01075 \text{ min}^{-1} \\k_2 &= 0.00163 \text{ min}^{-1} \\k_3 &= 0.00380 \text{ min}^{-1} \\k_4 &= 0.00464 \text{ min}^{-1}\end{aligned}$$

Having acquired positive results from the pseudoionone cyclization, which was in particular catalyzed by 85 percent solution of H_3PO_4 , cyclization catalyzed by H_3PO_4 -heterogeneous catalyst spread on kieselguhr was carried out.

The pseudoionone cyclization was carried out at the temperature of 80°C , catalyzed by 0.5 g of H_3PO_4 on kieselguhr containing approximately 40 percent H_3PO_4 per 0.0104 mol of pseudoionone with the molar ratio of pseudoionone:toluene 1:7. In comparison to the cyclization catalyzed by the sole H_3PO_4 , this cyclization had a slower course and gave a lower produced quantity of ionones, which was due to the effect of the produced side-products.

Conclusion

Utilizing the sole solid NaOH as the catalyst for the condensation of citral with acetone has not up to now been published. The accomplished experiments presented in this work conspicuously demonstrated that such catalyzed condensation result in the highest yield of pseudoionone ever published.

In regards to heterogeneous catalysts, the highest yield of pseudoionone was achieved in the case of using hydrotalcite with the molar ratio of Mg:Al 3:1. Basic reaction parameters affecting its course were studied and based on the acquired data; optimum conditions for the condensation were determined.

The presented text conspicuously refers to the maximum yields of pseudoionone, citing that the optimal conditions for the condensation catalyzed by NaOH include the temperature of 56°C , the molar ratio of citral:acetone:NaOH = 1:20:0.076 and the short reaction time of 15 min.

During cyclization of pseudoionone, the highest yields were acquired by the reaction catalyzed by use of 0.2 mol of 85 percent solution of H_3PO_4 at the temperature of 80°C with the molar ratio of pseu-

doionone:toluene 1:7. To summarize, in the optimal course of both of the reaction steps, theoretical yields of ionones as high as 91 percent can be achieved, whereas it includes 57.2 percent of α -ionone, 16.1 percent of β -ionone and 17.7 percent of γ -ionone.

Address correspondence to Libor Cervený, Department of Organic Technology, Institute of Chemical Technology, ITC Prague, Technická 5, 166 20 Prague 6, Czech Republic.

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