Heterogeneous Catalytic Synthesis of Zingerone and Dehydrozingerone

P. A. Chistyakova^{a, *}, A. V. Chistyakov^a, and M. V. Tsodikov^a

^aTopchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, Moscow, 119071 Russia *e-mail: polina.zharova@mail.ru Received March 26, 2020; revised May 5, 2020; accepted May 12, 2020

Abstract—Results of a single-stage heterogeneous catalytic synthesis of zingerone and dehydrozingerone have been described. The prospects of the proposed approach have been shown; the main kinetic laws governing the reaction have been revealed. Optimum conditions for zingerone and dehydrozingerone synthesis providing a yield of the target products of 45.8 and 76.2%, respectively, have been found.

Keywords: heterogeneous catalysis, copper, dehydrozingerone, zingerone **DOI:** 10.1134/S0965544120090066

Zingerone and dehydrozingerone are biologically active substances constituting ginger root [1]. These substances are commonly used in the food industry (as flavorings and conserving agents [2]) and the pharmaceutical industry: dehydrozingerone is used as an active component of anticonvulsants, an antioxidant, and an antimutagenic agent [3], while zingerone is an antioxidant and an antiinflammatory agent and exhibits activity in the suppression of enterotoxins (*Escherichia coli*) that cause diarrhea [4, 5] (this type of diarrhea is the main cause of infant mortality in developing countries [6]).

Zingerone and dehydrozingerone were first isolated from ginger root by Japanese chemist Hiroshi Nomura in 1917 [7]. In addition, Nomura has developed a synthetic method for zingerone synthesis by the hydrogenation of dehydrozingerone derived by the condensation of acetone and vanillin in the presence of alkalis (Scheme 1).



Scheme 1. Two-stage synthesis of zingerone.

Zingerone is still [8] produced by the two-stage method proposed by Nomura with the use of alkalis, which significantly increases the amount of waste and the cost of production [9]. Currently, attempts are being made to search for effective heterogeneous catalysts for the production of dehydrozingerone by the condensation of acetone with vanillin. A promising catalyst for the process is hydrotalcite, in the presence of which the dehydrozingerone yield achieves 88% within 4 h of the reaction [3].

It was previously found that primary alcohols can undergo heterogeneous catalytic cross-condensation with secondary alcohols [10]. This approach can be used to synthesize zingerone from vanillin and isopropanol in a single stage. A single-stage synthesis in the presence of supported catalysts will make it possible to exclude the hydrogenation stage and abandon the use of alkali at the first stage of condensation of vanillin with acetone.

This study is focused on the development of heterogeneous catalytic methods to produce valuable biologically active substances by the alkylation of vanillin with acetone or isopropanol. Results of a single-stage heterogeneous catalytic synthesis of zingerone and dehydrozingerone are described. Prospects of the proposed approach are shown; the main kinetic laws governing the reactions are revealed.

EXPERIMENTAL

Catalytic tests for the cross-condensation of vanillin with acetone and isopropanol in the presence of the synthesized systems were conducted on a Parr Series 5000 multiple reactor autoclave system. The test time under steady-state conditions was 5 h; stirring was implemented with a magnetic stirrer at a speed of 1000 rpm; the gas in the autoclave volume was argon under an initial pressure of 1 atm. Acetone and isopropanol were taken in a 15-fold molar excess with respect to vanillin.

Mono- and bimetallic catalysts Cu/Al_2O_3 , Ni/Al_2O_3 , $Ni-Cu/Al_2O_3$, $Fe-Cu/Al_2O_3$, and $Co-Cu/Al_2O$ with a metal content of 1 wt % were prepared by incipient wetness impregnation from solutions of respective nitrates (reagent grade); the support was γ -Al₂O₃ (AO Angarsk Plant of Catalysts and Organic Synthesis, 160 m²/g, 0.5-mm pellets). The synthesized samples were dried in a vacuum at 80°C for 5 h and then calcined in a muffle furnace at 500°C in an argon atmosphere for 5 h.

The qualitative composition of the liquid organic products was determined by chromatography-mass spectrometry on an Agilent MSD 6973 (HP-5MS column) and DelsiNermag Automass-150 instruments (CPSil-5 column) at an electron ionization of EI = 70 eV. The quantitative content of the liquid organic substances was determined by gas-liquid chromatography on a Varian 3600 instrument (Chromatec column, SE-30, 0.25 × 250 cm, Df = 0.3 mm, 50°C (5 min), 10 deg/min, 280°C , $T_{inj} = 250$ °C, $P_{inj} = 1$ bar, split ratio of 1/200, a flame ionization detector).

The acidic properties of the catalysts were studied by temperature-programmed desorption (TPD) of ammonia, which is used as a probe molecule, on an USGA gas chemisorption analyzer. A catalyst with a fraction of 0.25-0.5 mm and a weight of ~0.1 g (weighed portion was taken at an accuracy of 5×10^{-4} g) was placed in a quartz reactor on a layer of silica with a fraction of 1-0.5 mm. The sample was heated in a helium stream to a temperature of 500°C at a rate of 15 deg/min and calcined at this temperature in a helium stream for 1 h; after that, it was cooled to a temperature of 60°C. Next, the sample was saturated with ammonia in a stream of dried ammonia diluted with nitrogen for 20 min. Physically adsorbed ammonia was removed at 100°C in a dry helium stream for 1 h. After that, the sample was rapidly cooled in a dry helium stream (30 mL/min) to a temperature of 60°C. Analysis conditions: temperature increase to 600°C at a rate of 8°C/min in a helium stream at a flow rate of 30 mL/min.

RESULTS AND DISCUSSION

The laws governing the occurrence of two reactions—the condensation of vanillin and acetone (Scheme 2, reaction (1)) and vanillin and isopropanol (Scheme 2, reaction (2))—were studied. The catalysts were mono- and bimetallic systems based on γ -Al₂O₃ with supported copper particles and the iron triad metals, which previously proved to be highly active and selective in the condensation of oxygen-containing compounds [11–13]:



Scheme 2. Condensation of (1) vanillin with acetone to produce dehydrozingerone and (2) vanillin with isopropanol to produce zingerone.

Figure 1 shows dependences of vanillin conversion at a fixed temperature (180°C) on the nature of the supported metals. It is evident from the data in the figure that the most active metals are copper and nickel, which provide the maximum vanillin conversion. The catalysts based on iron and cobalt exhibit a significantly lower activity in the dehydrozingerone and zingerone synthesis reactions; therefore, Ni/Al_2O_3 and Cu/Al_2O_3 catalysts were selected for further studies.

PETROLEUM CHEMISTRY Vol. 60 No. 9 2020



Fig. 1. Vanillin conversion in the studied reactions in the presence of monometallic catalysts at a temperature of 180° C and a contact time of 3 h.

The temperature dependences of the dehydrozingerone and zingerone yields achieved during the condensation of vanillin with isopropanol and vanillin with acetone, respectively, are listed in Table 1.

It was found that the optimum temperature for dehydrozingerone synthesis is 180° C; it provides a maximum product yield in the presence of the studied catalysts. In the presence of the Ni/Al₂O₃ catalyst, the dehydrozingerone yield is more than 10% higher than the yield achieved in the presence of the Cu/Al₂O₃ catalyst (at 180°C); this fact indicates a higher activity of the nickel-containing system. However, an opposite picture is observed during the synthesis of zingerone:

in the presence of the Cu/Al_2O_3 catalyst, the target product yield is more than 10% higher than the yield obtained in the presence of the Ni/Al₂O₃ catalyst (at 245°C).

It is significant that, at temperature of 180° C, the zingerone yield is 40-50% lower than the dehydrozingerone yield; this fact apparently suggests that the reactions have different rate-limiting steps. With an increase in temperature to 245° C, the dehydrozingerone yield abruptly decreases owing to the vigorous formation of resinous nonvolatile compounds, which apparently are products of the polycondensation of vanillin and acetone (Scheme 3).



Scheme 3. Probable dehydrozingerone polycondensation route.

In the presence of the Cu/Al₂O₃ catalyst, an increase in temperature to 245° C leads to a 10% increase in the yield of zingerone synthesized from vanillin and isopropanol. In the presence of the Ni/Al₂O₃ catalyst, an increase in temperature increases the zingerone yield only slightly; in this case, the content of resinous nonvolatile compounds in the reaction products increases.

Thus, it was found that the most active catalyst of the samples studied in dehydrozingerone synthesis was the Ni/Al₂O₃ catalyst providing the target product yield of more than 87% at a temperature of 180°C. The most promising catalyst for zingerone synthesis from vanillin and isopropanol was the Cu/Al_2O_3 catalyst, in the presence of which the maximum zingerone yield of 45.8% at 245°C was achieved (Table 1).

Taking into account the fact that the catalyst systems tested in this study are supported catalysts, catalytic tests on the determination of the catalytic activity of the support (γ -Al₂O₃) were conducted (Table 2). It is evident from Table 2 that alumina is active in the conversion of acetone and vanillin to dehydrozingerone and almost inactive in the conversion of isopropanol and vanillin to zingerone. In the presence of alumina, the dehydrozingerone yield is lower than that in the presence of the metal-containing catalysts. At the

1082

Catalyst	Cu/Al ₂ O ₃	Ni/Al ₂ O ₃	Cu/Al ₂ O ₃	Ni/Al ₂ O ₃
temperature, °C	dehydrozingerone yield, %*		zingerone yield, %**	
130	16.0	18.1	4.2	1.5
180	76.2	87.5	36.3	31.6
245	20.4	17.3	45.8	35.2

Table 1. Temperature dependence of the dehydrozingerone and zingerone yields in the case of catalysis with 1 wt % Cu/Al_2O_3 and 1 wt % Ni/Al_2O_3 systems

* Dehydrozingerone is synthesized by reaction (1) shown in Scheme 2.

** Zingerone is synthesized by reaction (2) shown in Scheme 2.

same time, the variation in the dehydrozingerone yield in the presence of Al₂O₃ exhibits a symbatic dependence, which is shown in Table 1 for the supported catalysts. This fact suggests that a key factor in the condensation of acetone and vanillin is the acidity of the catalyst surface, whereas condensation is not the rate-limiting step for zingerone synthesis. It should be noted that, according to Scheme 2, one of the initial stages of zingerone synthesis is isopropanol dehydrogenation to acetone, which is apparently complicated in the presence of alumina without metal components. In addition, the main route of isopropanol conversion in the presence of unmodified alumina is isopropanol dehydration into propylene and diisopropyl ether. On the other hand, the low activity of alumina in zingerone synthesis can be attributed to the competing chemisorption of isopropanol and vanillin.

It is known that an important factor affecting the occurrence of chemical reactions is catalyst acidity [14–16]. To verify the effect of the acid–base properties of the support on the parameters of the studied reactions, catalytic tests on the synthesis of zingerone and dehydrozingerone in the presence of catalysts based on Sibunit and silica were conducted (Table 3).

It was found that, in the presence of the silicabased catalyst, the zingerone and dehydrozingerone yield abruptly decreases, while the Sibunit-based catalyst exhibits hardly any catalytic activity. Taking into account the surface factor, in this study, catalyst supports with a specific surface area that was close to or larger than the specific surface area of alumina (180– 230 m²/g) were tested (250–300 and 380–430 m²/g for SiO₂ and Sibunit, respectively). Thus, the decrease in catalytic activity in the order Cu/Al₂O₃ > Cu/SiO₂ > Cu/C is most probably attributed to a change in the surface acidity.

Table 2. Dehydrozingerone and zingerone yield in the presence of an Al_2O_3 catalyst support at a test time of 3 h

Temperature, °C	Dehydrozingerone yield, %	Zingerone yield, %
130	4.9	0.0
180	33.3	0.0
245	13.6	0.1

PETROLEUM CHEMISTRY Vol. 60 No. 9 2020

To determine the acidic properties of the studied catalysts, ammonia TPD studies were conducted; their results are shown in Fig. 2. It is evident from Fig. 2 that the alumina surface is capable of adsorbing a significantly larger number of ammonia probe molecules; this finding indicates the presence of a larger number of acid sites on the alumina surface. The Sibunit-based catalyst has hardly any ability to adsorb ammonia. Thus, the above assumption of the dependence of the catalyst activity in the condensation of acetone with vanillin to dehydrozingerone on the catalyst acidity is fully confirmed in the studies.

The next stage of the study was analysis the laws governing the synthesis of zingerone and dehydrozingerone in the presence of bimetallic catalysts. The use of bimetallic catalysts is a potentially promising field of catalysis, because different pairs of metals can exhibit a synergistic effect, which consists in an abrupt increase in their catalytic activity and/or selectivity in chemical reactions [17].

The catalytic test results showed that the introduction of iron or cobalt into the Cu/Al₂O₃ system leads to a decrease in catalytic activity in the synthesis of both dehydrozingerone and zingerone (Fig. 3). The use of a Ni–Cu/Al₂O₃ bimetallic system with different ratios of active components for the condensation of vanillin with acetone does not lead to visible changes in activity; moreover, the monometallic nickel catalyst exhibits a nearly identical activity. Thus, a key factor in dehydrozingerone synthesis from vanillin and acetone is, apparently, the acidity of the catalyst support. The deposition of nickel particles by the impregnation of alumina with nickel nitrate and subsequent calcining can lead to the formation of surface $Ni_xAl_{2x}O_4$ mixed oxide particles, which, in turn, can form a favorable acidity region for the occurrence of the condensation reaction. It should be noted that the ammonia TPD curves of "pure" alumina and alumina with deposited nickel particles are almost identical; this factor complicates the further analysis by this method.

In the case of using bimetallic systems for zingerone synthesis, it was found that the maximum target product yield is achieved in the presence of the Cu– Ni/Al_2O_3 system at a 1 : 1 molar ratio of components (Fig. 3). There is a large amount of published data on the formation of copper and nickel alloys on the sur-

Temperature	180°C	Temperature	245°C
catalyst	dehydrozingerone yield, %	catalyst	zingerone yield, %
Ni/Al ₂ O ₃	87.5	Cu/Al ₂ O ₃	45.8
Ni/SiO ₂	13.7	Cu/SiO ₂	9.4
Ni/C	0.4	Cu/C	0.1

Table 3. Dehydrozingerone and zingerone yield in the presence of catalysts based on the different supports

face of porous supports [18-20]. In general, the main factor affecting the catalytic properties of alloys is the electronic factor, i.e., a change in the energy of the *d*-band of the alloy compared with that of the individual metals [21].

The results show that, in the condensation of acetone with vanillin and isopropanol with vanillin, the main factor is the acidity of the catalyst and the hydrogenation—dehydrogenation activity of the supported active components, respectively. To confirm this conclusion, a kinetic analysis of the reactions was conducted to determine the apparent activation energies and compare them.

Figure 4 shows the kinetic curves of the conversion of vanillin reacting with isopropanol in the presence of a Ni–Cu/Al₂O₃ catalyst (initial vanillin concentration of 0.1 mol/L, 13-fold molar excess of isopropanol). Figure 5 shows the kinetic curves of the conversion of vanillin reacting with acetone in the presence of a Ni– Cu/Al₂O₃ catalyst (initial vanillin concentration of 0.1 mol/L, 13-fold molar excess of acetone). Calculations of the recorded kinetic curves showed that, for the condensation of vanillin with isopropanol and vanillin with acetone, a pseudo-zero and pseudofirst order of reaction with respect to vanillin, respectively, is observed. The data suggest that, in the case of the condensation of vanillin with acetone, vanillin and, apparently, acetone are chemisorbed by the catalyst surface; after that, they undergo a chemical reaction. In the reaction of vanillin with isopropanol, the pseudo-first order of reaction with respect to vanillin suggests that a probable rate-limiting step is isopropanol dehydrogenation on the catalyst surface.

The activation energy and preexponential factor for the studied reactions were calculated. In the synthesis of dehydrozingerone, the apparent activation energy was 80.3 kJ/mol and the preexponential factor was 1.3×10^6 . In the synthesis of zingerone, the apparent activation energy was 92.4 kJ/mol and the preexponential factor was 7.8×10^7 . The calculated activation energy values also indicate a high probability of different rate-limiting steps in the alkylation of vanillin with acetone or isopropanol.



Fig. 2. Temperature dependence of ammonia desorption rate for alumina, silica, and Sibunit.



Fig. 3. Yield of dehydrozingerone (at 180°C) and zingerone (at 245°C) in the presence of bimetallic catalysts at a test time of 3 h.



Fig. 4. Kinetic curves of the conversion of vanillin reacting with isopropanol in the presence of a $Ni-Cu/Al_2O_3$ catalyst (initial vanillin concentration of 0.1 mol/L, 13-fold molar excess of isopropanol).

CONCLUSIONS

The studies have shown the possibility of implementing the heterogeneous catalytic alkylation of vanillin with isopropanol and acetone to produce zingerone and dehydrozingerone, which are valuable biologically active substances constituting ginger root. It has been shown that nickel—copper catalysts are highly promising for a single-stage synthesis of zingerone from vanillin and isopropanol, without using alkalis and solvents. It has been found that, in the condensation of vanillin with acetone, the main factor affecting the catalyst activity is the catalyst acidity, while in the condensation of vanillin with isopropa-

PETROLEUM CHEMISTRY Vol. 60 No. 9 2020

nol, a fundamental role is played by the hydrogenation—dehydrogenation activity of the copper-containing active components. Kinetic studies have revealed the order of the studied reactions with respect to vanillin and the apparent activation energies. For the condensation of vanillin with acetone and vanillin with isopropanol, the apparent activation energy is 80.3 and 92.4 kJ/mol, respectively. The increase in the apparent activation energy for the condensation of vanillin with isopropanol is apparently attributed to a change of the rate-limiting step for another, which is characterized by a higher activation barrier to the reaction.



Fig. 5. Kinetic curves of the conversion of vanillin reacting with acetone in the presence of a $Ni-Cu/Al_2O_3$ catalyst (initial vanillin concentration of 0.1 mol/L, 13-fold molar excess of isopropanol).

FUNDING

This work was supported by the Russian Foundation for Basic Research, project no. 18-33-01068.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

REFERENCES

- 1. N. S. Mashhadi, R. Ghiasvand, G. Askari, et al., Int. J. Prev. Med. 4, 36 (2013).
- L. A. Svetaz, M. G. Di Liberto, M. M. Zanardi, et al., Int. J. Mol. Sci. 15, 22042 (2014).
- S. L. Bhanawase and G. D. Yadav, Curr. Catal. 6, 105 (2017).
- S. G. Shin, J. Y. Kim, H. Y. Chung, and J. C. Jeong, J. Agricul. Food Chem. 53, 7617 (2005).
- V. Mani, S. Arivalagan, A. I. Siddique, and N. Namasivayam, Mol. Cell. Biochem. 421, 169 (2016).
- J. C. Chen, L. J. Huang, S. L. Wu, et al., J. Agricul. Food Chem. 55, 8390 (2007).
- 7. H. Nomura, J. Chem. Soc. Trans. 111, 769 (1917).
- P. Van der Schaft, *Flavour Development, Analysis and Perception in Food and Beverages*, Ed. by J. K. Parker, J. S. Elmore, and L. Methven (Elsevier–WP, Amsterdam, 2015), p. 235.

- Z. Wang, G. Yin, J. Qin, et al., Synthesis 2008, 3675 (2008).
- A. V. Chistyakov, P. A. Zharova, S. A. Nikolaev, and M. V. Tsodikov, Catal. Today 279, 124, (2017).
- A. V. Chistyakov, S. A. Nikolaev, P. A. Zharova, et al., Energy 166, 569 (2019).
- P. A. Zharova, A. V. Chistyakov, M. V. Tsodikov, et al., Chem. Eng. Trans. 57, 31 (2017).
- P. A. Zharova, A. V. Chistyakov, M. V. Tsodikov, et al., Chem. Eng. Trans. 50, 295 (2016).
- 14. E. F. Iliopoulou, E. V. Antonakou, S. A. Karakoulia, et al., Chem. Eng. J. **134**, 51 (2007).
- 15. R. Kumar, S. Sithambaram, and S. L. Suib, J. Catal. **262**, 304 (2009).
- H. A. Benesi and B. H. C. Winquist, *Surface Acidity of Solid Catalysts* (Academic, New York, 1978).
- 17. O. G. Ellert, M. V. Tsodikov, S. A. Nikolaev, and V. M. Novotortsev, Usp. Khim. **83**, 718 (2014).
- S. D. Robertson, B. D. McNicol, J. H. de Baas, et al., J. Catal. 37, 424 (1975).
- 19. A. K. Singh and Q. Xu, ChemCatChem 5, 652 (2013).
- 20. J. H. Sinfelt, Acc. Chem. Res. 10, 15 (1977).
- I. Chorkendorff and J. W. Niemantsvedriet, *Concepts of* Modern Catalysis and Kinetics, 2nd Ed. (Wiley–VCH, Weinheim, 2007).

Translated by M. Timoshinina