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Catalytic Effect of Nanosized Metal Oxides on the Hantzsch Reaction

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Abstract—The effect of nanosized copper and aluminum oxides, which have a higher sorption capacity than that of bulk samples, on the Hantzsch reaction was studied. The adsorption of starting benzaldehydes and ethyl acetoacetate on the surface of copper and aluminum nanooxides resulted in the activation of these molecules and accelerated the Hantzsch reaction. In addition, considerable activation of ammonia and intermediates (chalcone and enamine) on the surface of aluminum nanooxide facilitated an increase in the rate and selectivity of the process. The experimental results were used to develop a one-pot method for the preparation of nifedipine and nitrendipine.

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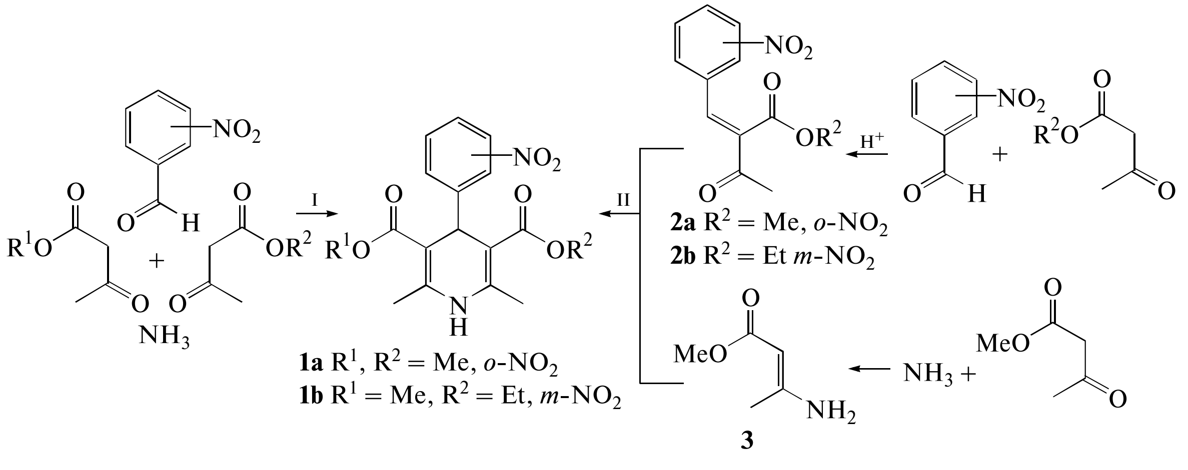
INTRODUCTION

The three-step Hantzsch reaction (see the scheme) is widely used in organic synthesis for the preparation of substituted dihydropyridines (**1a**, **1b**) from the series of nifedipine, which is a well-known drug used in the treatment of cardiovascular diseases [1]. However, the commonly used synthetic procedure is characterized by low selectivity, especially, with the use of nitro-substituted aromatic aldehydes. The reaction is performed stepwise with the isolation of intermediate enamine **3** and chalcone **2a** or **2b** (scheme, reaction path II); this considerably complicates the process and increases the consumption of solvents [2]. Therefore, a search for conditions and catalysts that make it possible to perform this reaction in a single step is promising.

In this work, we used nanosized metal oxides (nanooxides), which possess a highly developed surface and contained active sites of different nature, as catalysts for the three-component Hantzsch reaction [3]. We studied the sorption of reagents and Hantzsch reaction intermediates on the surface of copper and aluminum nanooxides. The experiments were performed with bulk and nanosized copper and aluminum oxides using an analysis of the diffuse reflectance IR spectra. The composition of crude Hantzsch reac-



Scheme. Reaction scheme of the preparation of nifedipine (**1a**) and nitrendipine (**2b**) (I) with the use of the three-component Hantzsch reaction and (II) the conventional three-step procedure tion products was studied using ^1H NMR spectroscopy and HPLC.

EXPERIMENTAL

Methanol (98%), an aqueous ammonia solution (30%), 2-nitrobenzaldehyde (99%), 3-nitrobenzaldehyde (99%), and methyl 3-aminocrotonate (enamine) (97%) from Lancaster and ethyl acetoacetate (99%) and methyl acetoacetate (99%) from Acros Organics were used in this study. Nanosized copper oxide (particle size of 50–80 nm) and nanosized aluminum oxide (particle size of 20–50 nm), which were prepared using a gas-phase procedure at the Institute of Metal Physics, Ural Division, Russian Academy of Sciences (Laboratory of Prof. A.E. Ermakov), were used as catalysts [4].

The melting points measured on combined Boetius plates were uncorrected. The diffuse reflectance spectra were measured on a Spectrum One FTIR spectrometer (Perkin Elmer) using an automated diffuse reflectance attachment. The ^1H NMR spectra were obtained on an AVANCE DRX-400 spectrometer (Bruker) with an operating frequency of 400 MHz.

The Hantzsch reaction was performed by heating a reaction mixture with an aldehyde : methyl acetoacetate : ammonia : metal nanooxide ratio of 1 : 2 : 1 : 0.1 (in the preparation of nifedipine) or an aldehyde : ethyl acetoacetate : methyl acetoacetate : ammonia : metal nanooxide ratio of 1 : 1 : 1 : 1 : 0.1 (in the preparation of nitrendipine) in methanol. Then, the reaction mixture was evaporated, and the resulting crude product was analyzed by ^1H NMR spectroscopy and HPLC (a normal-phase LiChrosorb Si 60 column; mobile phase, a mixture of hexane with isopropanol in a ratio of 9 : 1). The retention times (min) were the following: 18.70, nifedipine; 42.70, nitrendipine; 25.24, chalcone; and 16.12, enamine.

*Dimethyl 2,6-Dimethyl-4-(2-Nitrophenyl)-1,4-Dihydropyridine-3,5-Dicarboxylate (Nifedipine) (**1a**)*

After recrystallization from ethanol, the yield of the product with mp 165°C was 67%. ^1H NMR spectrum (δ, ppm): 2.25 (s, 6H, CH_3); 3.51 (s, 6H, OCH_3); 5.49 (s, H); 7.34–7.59 (m, 4H, Ar); 9.00 (s, H, NH).

*Methyl Ethyl 2,6-Dimethyl-4-(2-Nitrophenyl)-1,4-Dihydropyridine-3,5-Dicarboxylate (Nitrendipine) (**1b**)*

After extraction with chloroform and precipitation with methanol, the yield of the product with mp 130–132°C was 50%. ^1H NMR spectrum (δ, ppm): 1.16 (t, 3H, $C\underline{H}_3CH_2$, $J = 7.0$ Hz); 2.25 (s, 6H, CH_3); 3.51 (s, 3H, $-OCH_3$); 3.98 (t, 2H, $CH_3C\underline{H}_2$, $J = 7.0$ Hz); 4.99 (s, H); 7.52–8.01 (m, 4H, Ar); 9.07 (s, H, NH).

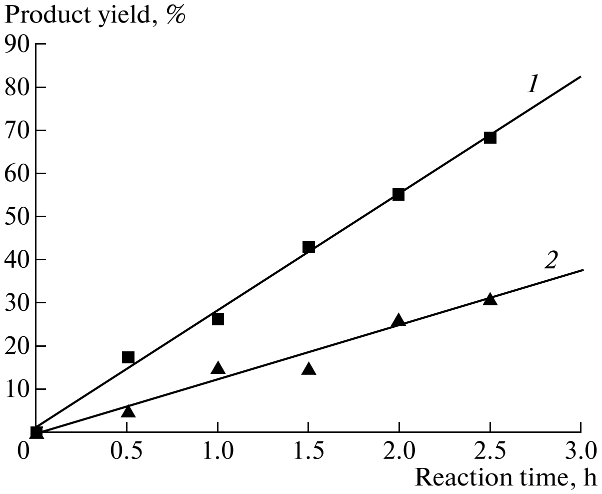


Fig. 1. Yields of nifedipine (according to HPLC data) (*1*) in the presence and (*2*) in the absence of aluminum nanooxide.

*Ethyl 2-Acetyl-3-(3-Nitrophenyl)-Acrylate (Chalcone) (**2b**)*

3-Nitrobenzaldehyde (3.3 mmol, 0.5 g), ethyl acetoacetate (9.9 mmol, 1.15 g), nanosized Al_2O_3 (1.1 mmol), morpholine (3.3 mmol), and acetonitrile (5 ml) were mixed. The reaction mass was kept with stirring at 60°C for 6 h with a reflux condenser; thereafter, crystallization from ethanol was performed. The yield of the product with mp 109°C was 74%.

For $C_{13}H_{13}O_5N$ anal. calcd. (%):	C 59.32;	H 4.94;	N 5.32.
Found (%):	C 59.11;	H 4.97;	N 5.29.

^1H NMR spectrum (δ, ppm): 1.31 (t, 3H, J = 7.16 Hz, $C(O)CH_2C\underline{H}_3$); 2.45 (s, 3H, CH_3); 4.38 (kv, 2H, J = 7.16 Hz, $C(O)C\underline{H}_2CH_3$); 7.59 (s, H, –CH=); 7.60 (t, H, J = 7.8 Hz, C(5)Ar); 7.76 (d, H, J = 7.8 Hz, C(6)Ar); 8.26 (dd, H, J = 7.8 Hz, C(4)Ar); 8.34 (s, H, C(2)Ar).

Methyl 3-Aminocrotonate (Enamine) (3)

^1H NMR spectrum (δ, ppm): 1.90 (s, 3H, $OC\underline{H}_3$); 3.64 (s, 3H, CH_3); 4.52 (s, H, CH=); 4.8 (br s, H, NH_2); 7.9 (br s, H, NH_2).

The sorption of starting compounds and Hantzsch reaction intermediates on metal nanooxides was performed in methanol solutions at a sorbate : sorbent molar ratio of 1 : 3 followed by the removal of the solvent.

RESULTS AND DISCUSSION

The use of aluminum nanooxide allowed us to perform a three-component version of the synthesis of nifedipine (scheme, reaction path I); in this case, the yield of the target product was increased by a factor of more than 2 (Fig. 1). The use of aluminum nanooxide in the synthesis of nifedipine made it possible to obtain this compound in 60% yield (according to HPLC data) from four components in a single step. In the presence of copper nanooxide, catalytic effects of this kind were not observed.

Moreover, aluminum nanooxide optimizes the step of chalcone formation (scheme, reaction path II); the yield of chalcone increases from 48 to 74%. Thus, the use of aluminum nanooxide has a favorable effect on the commonly used procedure for the synthesis of nitrendipine.

A comparison of diffuse reflectance IR spectra indicated that the absorbance of copper nanooxide decreased, as compared with that of a bulk sample, and the absorption bands of Cu–O shifted by 10–15 cm^{-1} to the high-frequency region. Previously, in a study of copper nanooxide with the use of probe molecules [4], we found that Cu^+ and Cu^{2+} Lewis acid sites are the active sites of the surface. The Lewis base sites are the oxygen atoms of the oxide and hydroxyl groups and ion pairs like M^{n+}–O^-. The Brønsted acid sites are the protons of the hydroxyl groups of copper hydroxy carbonate, which is formed upon the sorption of carbon dioxide on the nanooxide surface. The occurrence of an unresolved absorption band with maximums at 601 and 547 cm^{-1} in the spectrum of a sample used as a catalyst for the Hantzsch reaction suggests the presence of a considerable amount of copper(II) oxide along with copper(I) oxide in this sample. Other spectroscopic characteristics are also consistent with the results reported previously [4].

The aluminum nanooxides prepared by a gas-phase procedure can occur in various structural modifications [3]. In this work, we used a material whose structure was close to α-Al_2O_3, as judged from the character of its spectrum. According to published data [5], both AlO_6 octahedrons and Al atoms with a lower coordination number occur in its structure. In the spectrum of nanodispersed powder, the absorption bands of both of the polyhedrons are shifted by 30–50 cm^{-1} to the region of smaller wavenumbers, as compared with published data [5]. The surface of aluminum nanooxide is a set of Al^{3+} central atoms in an environment of oxygen atoms (ν_{Al-O} = 960, 710, and 685 cm^{-1}) and coordinated water molecules (ν_{OH} = 3472–3515 cm^{-1}, δ_{H_2O} = 1620–1640 cm^{-1}).

To study the Hantzsch reaction mechanism in the presence of nanosized metal oxides by diffuse reflectance IR spectroscopy, we examined the sorption of reactants and reaction intermediates on the surfaces of copper and aluminum oxides. The IR spectra of benzaldehydes sorbed on the surface of metal nanooxides exhibited a change in the spectroscopic characteristics corresponding to the vibrations of both the carbonyl fragment of the aldehyde group (see the table) and the M–O bonds of oxides. The $\nu_{C=O}$ bands of benzaldehyde sorbed on copper and aluminum oxides shifted by 156 and 150 cm^{-1}, respectively. In this case, ν_{CuO} and ν_{AlO} band maximums also shifted differently (by 47 and 43 cm^{-1}, respectively). These changes can be a consequence of the coordination of the oxygen atom of the carbonyl group of benzaldehyde to the Lewis site of the sorbent (metal oxide cation); in turn, this increases a positive charge at the carbon atom of the carbonyl group.

Main absorption bands (cm^{-1}) in the IR spectra of free and sorbed aldehydes

Sorbent	Benzaldehyde		*ortho*-Nitrobenzaldehyde			*meta*-Nitrobenzaldehyde		
	$\nu_{skeleton}$ (C=C)	$\nu_{C=O}$ (HC=O)	$\nu_{skeleton}$ (C=C)	ν_a (NO_2), ν_s (NO_2)	$\nu_{C=O}$ (HC=O)	$\nu_{skeleton}$ (C=C)	ν_a (NO_2), ν_s (NO_2)	$\nu_{C=O}$ (HC=O)
Without a sorbent	1597	1703	1607	1514	1687	1615	1531	1691
	1584		1573	1359		1583	1347	1703
	1455		1448			1471		
Nano-CuO	1593	1547	1595	1529	1395	1615	1532	1704
	1543		1569	1395		1583	1353	
	1448		1448			1478		
Nano-Al_2O_3	1602	1553	1605	1535	1701	1479	1539	1707
			1573	1348			1358	
			1480					
Bulk Al_2O_3	1600	1549	1605	1526	1702	1582	1582	1703
			1573	1346		1477	1477	
			1480					

Note: ν_a and ν_s refer to antisymmetrical and symmetrical stretching vibrations, respectively.

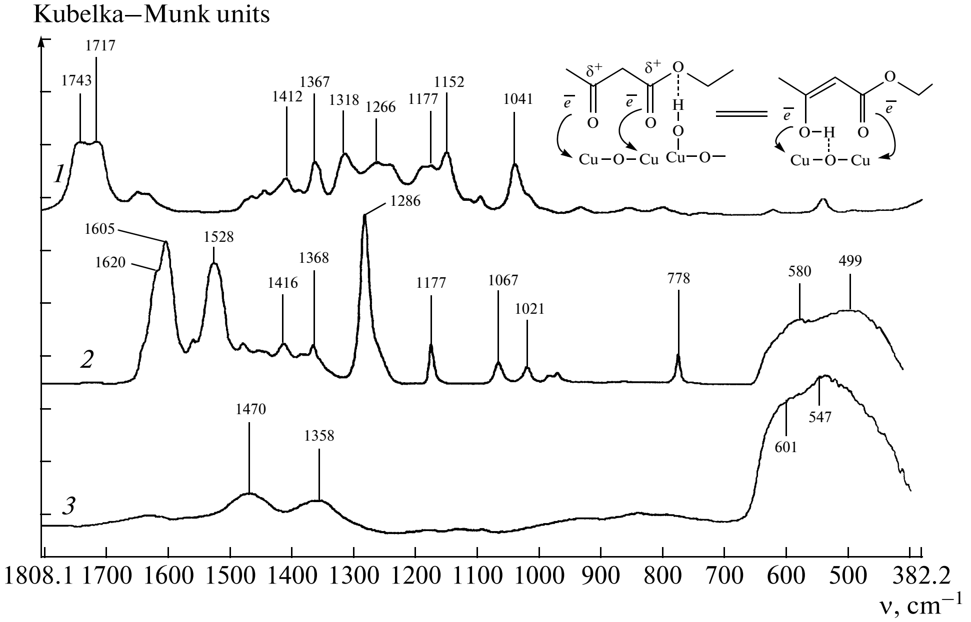


Fig. 2. Scheme of the interaction of ethyl acetoacetate with copper nanooxide and the IR spectra of (*1*) ethyl acetoacetate, (*2*) ethyl acetoacetate sorbed on copper oxide, and (*3*) copper oxide.

A comparison between bulk and nanosized aluminum oxides indicates that, in the IR spectrum of benzaldehyde sorbed on a nanosized sample, the absorption band intensity ratio is $\nu_{C=O}/\nu_{Al-O} = 0.081$, whereas it is 0.014 in the spectrum of bulk aluminum oxide. The experimental results can be explained by an increase in the sorption capacity of nanosized metal oxide, as compared with a standard sample.

The sorption of *ortho*-nitrobenzaldehyde on the surface of copper nanooxide was accompanied by the disappearance of an absorption band due to the vibrations of the carbonyl group and a considerable increase in the intensity and a shift of absorption bands due to nitro groups toward low frequencies. It is likely that absorption bands due to the vibrations of the NO_2 group and the C=O group coordinated to the copper atom superimposed on each other (see the table). This is supported by a shift of the absorption band due to the Cu–O bond to a low-frequency region by more than 30 cm^{-1}. Evidently, a weaker interaction occurred in the case of aluminum oxide.

Upon the coordination of *meta*-nitrobenzaldehyde to the surface of nanooxides, absorption bands corresponding to the skeleton vibrations of the benzene ring changed, whereas the absorption bands of carbonyl and nitro groups remained almost unchanged. This fact suggest the interaction of the π-electron system of the ring with the Lewis base sites of the oxide surface.

Upon the sorption of *ortho*- and *meta*-nitrobenzaldehydes on bulk aluminum oxide (a sorbent : sorbate ratio of 3 : 1), the IR spectra exhibited bands due to the vibrations of groups belonging to the initial aldehydes; however, a change in the sorbent : sorbate ratio to 9 : 1 resulted in the appearance of absorption bands due to only sorbed aldehydes. At the same time, the complete sorption of the above aldehydes occurred on the surface of aluminum nanooxide at a sorbent : sorbate ratio of 3 : 1.

In any event, the sorption of benzaldehyde, as well as *ortho*- and *meta*-nitrobenzaldehydes, on the surface of copper or aluminum nanooxides caused an increase in the positive charge on the carbon atom of the carbonyl group; this could increase the reactivity of benzaldehyde in the Hantzsch reaction.

As can be seen in Fig. 2, the sorption of ethyl acetoacetate was accompanied by a change in the frequency characteristics of the vibrations of bonds in both of the carbonyl groups ($\nu_{C=O}$) and the vibrations of the C–O–C unit. In addition, a low-frequency shift and an increase in the intensity of the $\nu_{C=C}$ band of the enol form of the sorbate occurred, as well as a broadening and shift of the ν_{Cu-O} band of the sorbent. Evidently, the donor–acceptor interactions of the C=O, COO, and C=C fragments of ethyl acetoacetate with the surface active sites of copper and aluminum nanooxides (M^{n+}, –OH) resulted in the formation of polarized chelate-like structures, including those with a strained bond. However, note that the shift of sorbent absorption bands in copper nanooxide was greater than that in aluminum nanooxide.

Upon the sorption of ammonia on the surface of copper nanooxide, almost no changes were detected in the spectroscopic characteristics, whereas they were considerable on the surface of aluminum nanooxide (Fig. 3). In the IR spectrum of an aqueous solution of ammonia, symmetrical deformation vibrations of the

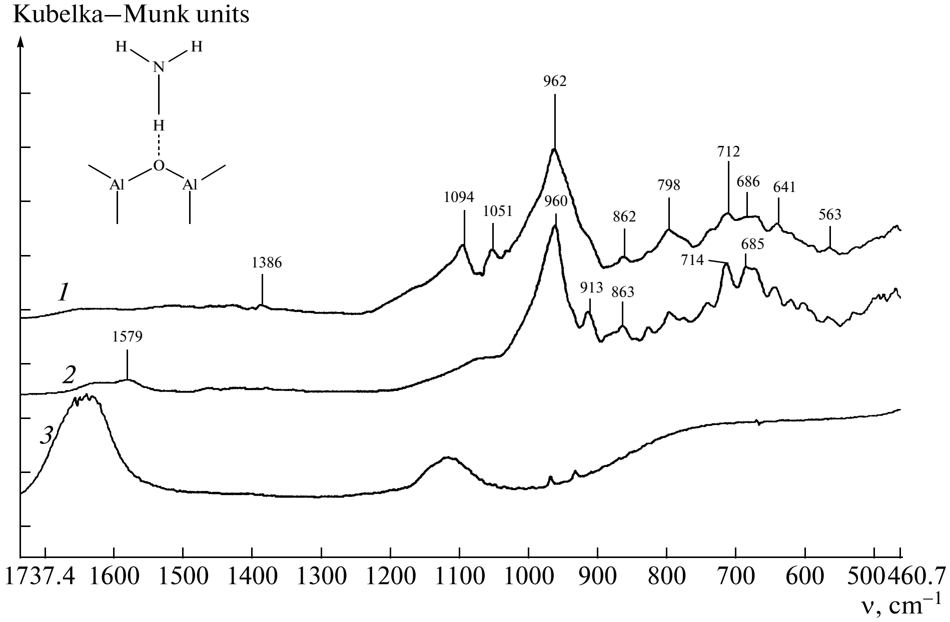


Fig. 3. Scheme of the interaction of an aqueous solution of ammonia with aluminum nanooxide and the IR spectra of (*1*) aluminum oxide, (*2*) ammonia sorbed on aluminum oxide, and (*3*) ammonia solution.

distorted pyramidal NH_3 molecule manifested themselves at 1160 cm^{-1}, whereas the spectrum of the substrate sorbed on the surface of aluminum nanooxide exhibited bands at 1579 (δ_{HNH}), 1342, 913, and 740 cm^{-1} and a shoulder at 1070 cm^{-1} (ρ_{NH_2}). This suggests an elongation of the $H–NH_2$ bond, probably, due to the interaction of a hydrogen atom with strong Lewis base sites of the surface; as a result of this, a weakening of the H–N bond occurred to facilitate the activation of ammonia in the Hantzsch reaction. The appearance of additional absorption bands at 600–800 cm^{-1} can be explained by the formation of additional Al–OH groups. As for Al–O bonds, the intensity of an absorption band at 960 cm^{-1} increased with reference to a doublet at 714 and 685 cm^{-1}. This can be a consequence of an increase in the number of coordinatively unsaturated aluminum atoms—surface active sites. Thus, the catalytic activity of aluminum nanooxide in the Hantzsch reaction in the absence of the activity of copper nanooxide in this reaction can be explained by differences in the sorption of ammonia on their surfaces.

The study of the sorption of enamine **3** and chalcone **2b** on aluminum nanooxide indicated that the coordination of **2b** was accompanied by a decrease in the number of absorption bands, a shift in frequencies, and a redistribution of intensities in the absorption region of carbonyl groups (1730–1620 cm^{-1}) and in the region of Al–O vibrations (Fig. 4). This allowed us to hypothesize that the aluminum atoms of the nanooxide participate in the formation of a chelate-like complex with carbonyl and ester groups. At the same time, the disappearance of absorption bands due to free surface hydroxyl groups at 3693 cm^{-1} and changes in the region of the vibrations of bridging C–O–C groups (1000–1200 cm^{-1}) suggest the occurrence of a hydrogen bond between these groups.

A considerable number of poorly resolved absorption bands in the spectrum of intermediate **3** (Fig. 5) suggests the presence of tautomeric forms in which this compound occurs. In particular, in the range of 1800–1500 cm^{-1}, both the vibrations of carbonyl groups with various degrees of binding and the $\nu_{C=C}$ and $\nu_{C=N}$ vibrations can manifest themselves. Upon sorption on aluminum nanooxide, all of the bands in this region shifted toward low frequencies, and a redistribution of their intensities occurred. In addition, changes were observed in the region of the vibrations of bridging C–O–C groups (1100–1250 cm^{-1}), which are indicative of changes in bond parameters and the electronic state of the carbonyl group because of its interaction with surface aluminum atoms. Simultaneously, a shift in the absorption band maximums of Al–O bonds and a redistribution of their intensity occurred. This can be a consequence of a change in the symmetry of the nearest environment of aluminum atoms on the surface of nanopowder. A weak absorption band due to free surface hydroxyl groups disappeared from the high-frequency region. Because of the superposition of absorption bands due to the stretching vibrations of water and –NH and NH_2 groups, the shape of the overall band changed with the appearance of two absorption maximums of N–H bonds shifted to the low-frequency region (at 3319 cm^{-1} and a shoulder at 3435 cm^{-1}). The above

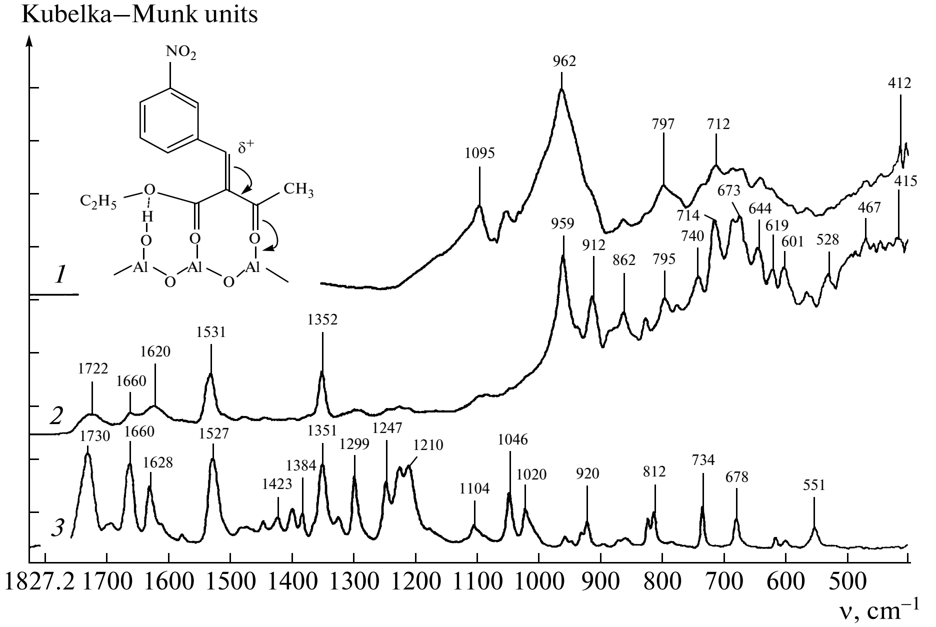


Fig. 4. Scheme of the interaction of intermediate **2b** with aluminum nanooxide and the IR spectra of (*1*) aluminum oxide, (*2*) intermediate **2b** on aluminum nanooxide, and (*3*) intermediate **2b**.

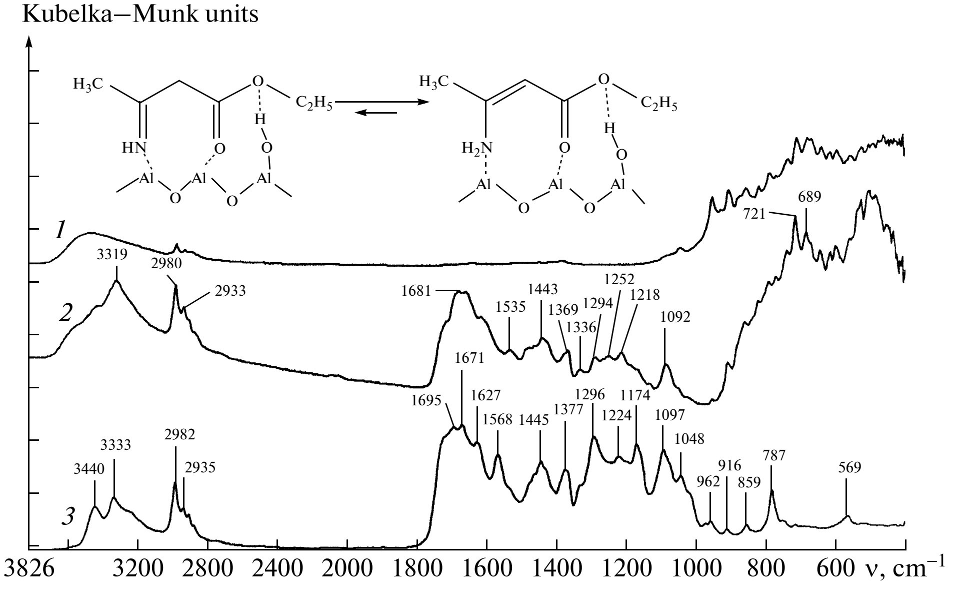


Fig. 5. Scheme of the interaction of compound **3** with the surface of aluminum nanooxide and the IR spectra of (*1*) aluminum oxide, (*2*) compound **3** on aluminum oxide, and (*3*) compound **3**.

changes in $\nu_{C=C}$ and $\nu_{C=N}$ are a consequence of the coordination of the nitrogen atom and the formation of a hydrogen bond with the oxygen atoms of aluminum oxide. Figure 5 shows a hypothetical scheme of the interaction of Hantzsch reaction intermediate **3** with aluminum oxide.

Thus, an analysis of spectroscopic data concerning the interaction of reagents participating in the Hantzsch reaction and intermediates on the surface of metal nanooxides allowed us to explain the reason for different activities of copper and aluminum nanooxides in this reaction. Aluminum nanooxide is a more efficient catalyst because it activates initial reactants (nitro-substituted benzaldehyde, ethyl acetoacetate, and, especially, ammonia) and increases the reactivity of intermediate enamine **3** and chalcone **2b**; because of this the rate of the Hantzsch reaction increases in the presence of this oxide.

In addition, the analysis of the crude products of the synthesis of nifedipine and nitrendipine by ^{1}H NMR spectroscopy and HPLC suggests a considerable decrease in the amount of impurities in the target products prepared under conditions of heterogeneous catalysis; because of this, the additional purification of the target compounds is not required.

The above experiments make it possible to use a single-step four-component procedure for the synthesis of nitrendipine or to optimize a commonly used three-step procedure. We developed a one-pot method for the preparation of nifedipine in >60% yield. The above experimental results show promise for the further optimization of the method for the synthesis of nifedipine and its analogs.

ACKNOWLEDGMENTS

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