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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Catalytic Effect of Nanosized Metal Oxides on the Knoevenagel Reaction

Yu. A. Titova, O. V. Fedorova, I. G. Ovchinnikova, G. L. Rusinov, and V. N. Charushin

Postovskii Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences, Yekaterinburg, Russia
e-mail: titova@ios.uran.ru

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Abstract—The effect of nanosized metal oxides (Al, Mg, Cu, Ni oxides) on the synthesis of chalcones that are key intermediate in the synthesis of Nitrendipine and Felodipine drugs was examined.

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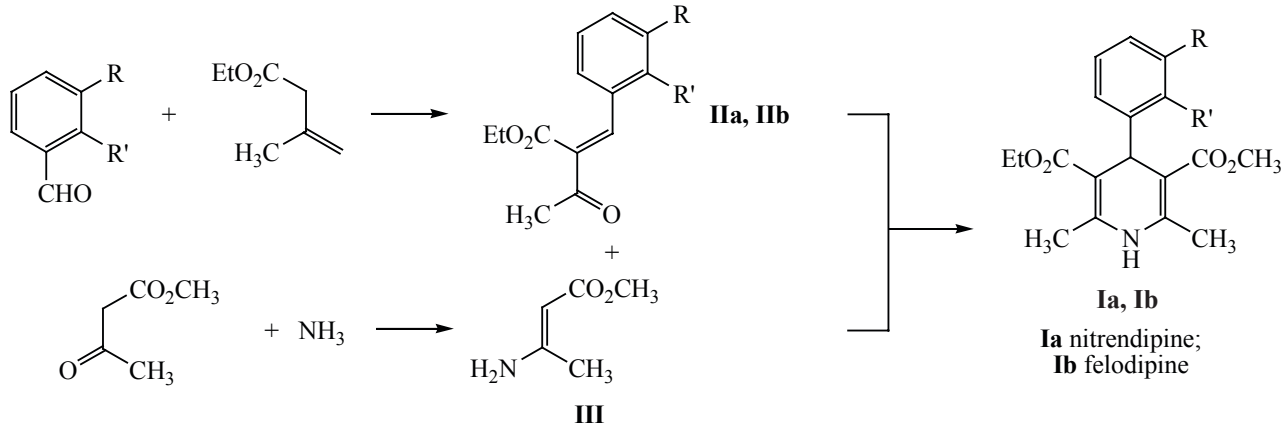
Substituted dihydropyridines Ia and Ib of the Nifedipine series are widely used in medical practice for the treatment of cardiovascular diseases [1]. Industrial synthesis of these substances is multistep:



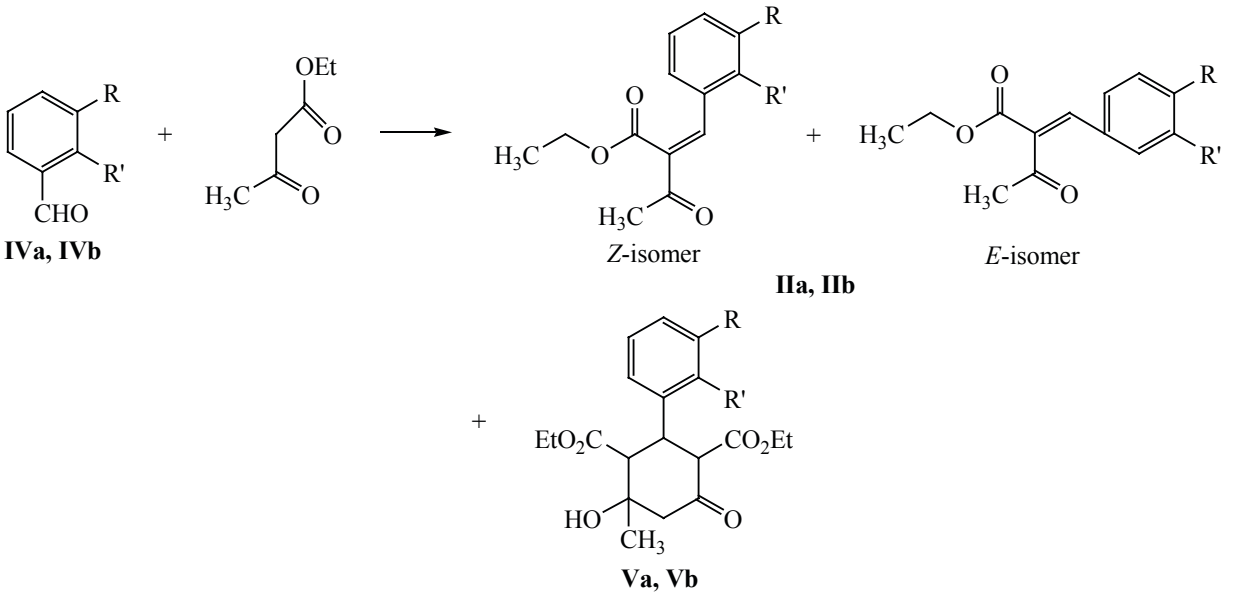
where R = NO_2, R' = H (**Ia, IIa**); R = R' = Cl (**Ib, IIb**). The synthesis of benzylidene intermediate **II** (Knoevenagel reaction) is the most labor-consuming and expensive step. The reaction is performed in alcohol on heating in the presence of two catalysts (a weak base and a weak acid); the yield is 70–80% [2, 3]. Procedures have been suggested for performing Knoevenagel condensation using Lewis acids ($TiCl_4$, $ZnCl_2$, $HClO_4$–SiO_2) [4–6], ionic liquids [7], heterogeneous catalysts (zeolites, clays, supported organic catalysts) [8, 9], and ultrasonic and microwave radiation [10, 11]. Some of the suggested procedures are indeed efficient and ensure high yields of the target product. However, complex structure, difficult availability, and high cost of the majority of the catalysts do not allow these procedures to become generally accepted in industry and in laboratory practice.

The effect of nanosized metal oxides having highly developed surface and containing various active sites on the regio- and stereoselectivity of the Nitrendipine synthesis was examined. It was shown that nanosized alumina activates the starting reactants in the Hantzsch synthesis (nitro-substituted benzaldehyde, acetoacetic acid ester, and especially ammonia) and enhances the reactivity of the intermediate chalcone **II** and enamine **III** [12].

In this study we examined the effect of nanosized metal oxides on the synthesis of the key intermediate of the Nitrendipine synthesis, chalcone **IIa** (R = 3-NO_2), and optimized the conditions of its preparation. We found that, under the conditions of heterogeneous catalysis, the reaction yields cyclohexanone **Va** as by-product.

The ratio of the starting aldehyde **IVa**, target product **IIa**, and by product (cyclohexanone **Va**) and the isomer ratio were determined from the integral intensities of the characteristic proton signals in the ^{1}H NMR spectrum (Table 1):

where R = NO_2 (**IIa**, **IVa**, **Va**); R = R' = Cl (**IIb**, **IVb**, **Vb**).



Because the catalytic properties of nanosized metal oxide can depend on feature of the metal, we performed experiments with a series of nanosized oxides (Cu, Al, Mg, Ni oxides). For comparison, we examined the catalytic properties of bulk aluminum and magnesium oxides. We found that nanosized metal oxides are more effective catalysts of the Knoevenagel reaction compared to bulk oxides (Table 2, entry nos. 1, 17–19). This can be attributed to the more developed surface of nanosized oxides, to the presence of a large amount of active surface groups, and hence to high sorption power, compared to bulk samples. Nanosized alumina appeared to be the best (Table 2, entry no. 1). In the presence of nanosized magnesia, relatively large amount of the by-product, cyclohexanone **Va**, is formed along with the desired chalcone **IIa**; furthermore, a large amount of the starting aldehyde remains unchanged. Nanosized copper and nickel oxides probably form a complex with **IIa**, because in the ^{1}H NMR spectra all the signals are broadened.

Table 1. Characteristic proton signals of **IIa**, **IVa**, and **Va**

Compound	Proton signal, δ, ppm				
	HC=O	–CH_2–CH_3	–CH_2–CH_3	CH	Me
IVa	10.16	–	–	–	–
IIa	–	4.28 q	*Z*-Isomer 1.21 t *E*-Isomer 1.29 t		*Z*-Isomer 2.49 s *E*-Isomer 2.40 s
Va	–	3.83; 3.94 m	0.86; 0.96 t	5.13 s	1.30 s

Table 2. Optimization of the synthesis of **IIa**

Entry no.	τ, h	*T*, °C	Solvent	Nanosized metal oxide (0.1 mol)	Catalyst (0.1 mol)	Relative content of chalcone **IIa**, % (ratio of *E* and *Z* isomers)	Yield of cyclohexanone **Va**, %
1	20	60	CH_3CN	Al_2O_3	Morpholine	87.5 (1.0:4.5)	Traces
2	20	60	CH_2CI_2	Al_2O_3	Morpholine	84.8 (1.0:3.7)	Traces
3	20	60	C_6H_6	Al_2O_3	Morpholine	75.8 (1.0:4.1)	Traces
4	20	60	THF	Al_2O_3	Morpholine	66.6 (1.0:3.3)	13.3
5	20	60	DMF	Al_2O_3	Morpholine	60.6 (1.0:2.4)	18.8
6	20	60	H_2O	Al_2O_3	Morpholine	50.0 (1.0:2.0)	22.5
7	20	60	CH_3OH	Al_2O_3	Morpholine	49.3 (1.0:2.0)	34.9
8	20	60	CH_3CN	Al_2O_3	HCl	72.4 (1.0:2.3)	None
9	20	60	CH_3CN	Al_2O_3	Acetic acid	44.7 (1.0:1.5)	Traces
10	20	60	CH_3CN	Al_2O_3	Anabasine	33.3 (1.0:2.0)	36.4
11	20	60	CH_3CN	Al_2O_3	Pyridine	26.6 (1.0:2.4)	None
12	20	60	CH_3CN	Al_2O_3	No catalysts	8.0 (1.0:7.0)	None
13	10	60	CH_3CN	Al_2O_3	Morpholine	71.9 (1.0:4.2)	Traces
14	30	60	CH_3CN	Al_2O_3	Morpholine	82.6 (1.0:6.5)	Traces
15	50	60	CH_3CN	Al_2O_3	Morpholine	89.2 (1.0:4.0)	Traces
16	20	60	CH_3CN	No n/o	Morpholine	78.1 (1.0:3.1)	8.6
17	20	60	CH_3CN	Bulk Al_2O_3	Morpholine	70.9 (1.0:3.7)	Traces
18	20	60	CH_3CN	MgO	Morpholine	22.5 (1.0:1.0)	45.9
19	20	60	CH_3CN	Bulk MgO	Morpholine	45.8 (1.0:2.7)	27.5
20	20	60	CH_3CN	NiO	Morpholine	All signals are broade	
21	20	60	CH_3CN	CuO	Morpholine	The same	
22	20	40	CH_3CN	Al_2O_3	Morpholine	96.2 (1.0:3.7)	Traces
23	20	22	CH_3CN	Al_2O_3	Morpholine	77.5 (1.0:4.0)	Traces
24	40	40	CH_3CN	Al_2O_3	Morpholine	96.3 (1.0:3.7)	Traces

We found that, in the presence of nanosized alumina, *Z*-isomer of **IIa**, whose structure is the most favorable for the formation of *S*-enantiomer of Nitrendipine [12], is always formed in excess.

As seen from Table 2, the best solvent for the Knoevenagel reaction is acetonitrile. With strongly polar solvents such as methanol, DMF, and water, the reaction direction is shifted toward formation of cyclohexanone **Va** by attack of one more acetoacetic acid ester molecule on chalcone **IIa**, followed by condensation.

Despite the fact that, according to published data, the Knoevenagel reaction occurs under basic conditions, under the conditions of heterogeneous catalysis, namely, in the presence of nanosized alumina, the reaction is catalyzed by both the base and the acid. Acid catalysts ensure excellent regioselectivity of the process (Table 2, entry nos. 8 and 9). It is interesting that, in the presence of the commonly used catalyst of the Knoevenagel reac-

tion, pyridine, the yield of the target product was as low as 26.6% (Table 2, entry no. 11), with the crude product free of even traces of side cyclohexanone, according to the ^{1}H NMR data. Structurally related anabasine showed not only low yield, but also low regioselectivity of the reaction (36.4% cyclohexanone, Table 2, run no. 10). Morpholine showed better catalytic properties in the presence of nanosized alumina (Table 2, run no. 1).

As expected, the target product yield increased with an increase in the reaction time (Table 2, run nos. 13–15). At temperatures over 60°C, the starting reactants practically fully transform into the undesirable by-product, cyclohexanone. The highest yield of chalcone **IIa** was attained at 40°C (Table 2, run no. 22).

In some experiments, we found that a decrease in the solvent volume leads to a decrease in the reaction time. The reaction is more complete at the solvent volume sufficient only for dissolving the starting reactants.

Thus, the optimal conditions for preparation of chalcone **IIa** are morpholine and nanosized alumina as catalysts, temperature of 40°C, acetonitrile as solvent, and reaction time of 20 h.

In addition, we examined the possibility of preparing under similar conditions compound **IIb**, a key intermediate in the synthesis of Felodipine drug. We found that, when the reaction was performed under the above-described conditions at 40°C, the major product (yield 85%) was cyclohexanone Vb. At the process temperature decreased to 22–25°C, the process became fully regiospecific, because the ^{1}H NMR spectra of crude product **IIb** contained only signals from the target chalcone, with no signals from the starting aldehyde **IVb** and side cyclohexanone **Vb**. The *E* to *Z* isomer ratio for **IIb** was 1.0 : 2.4.

EXPERIMENTAL

Experiments were performed with 3-nitrobenzaldehyde (99%), 2,3-dichlorobenzaldehyde (99%), (–)-anabasine (94%; Lancaster), ethyl acetoacetate (99%), morpholine (98%), and pyridine (98%; Acros Organics). As catalysts we took Al_2O_3 (analytically pure grade) and MgO (chemically pure grade) produced by Khimsnab association and nanosized Al_2O_3, MgO, NiO, and CuO (particle size 50−80 nm) prepared by the gas-phase procedure [13].[1]

The melting points measured with combined Boëtius stages were not subjected to additional correction. The ^{1}H NMR spectra were recorded with an Avance DRX-400 spectrometer (Bruker) operating at 400 MHz.

Preparation of chalcones II (general procedure). Appropriate aldehyde, ethyl acetoacetate, nanosized metal oxide, and catalyst were mixed in 1 : 1 : 0.1 : 0.1 molar ratio, and the solvent was added. The mixture was stirred at the required temperature in a flask equipped with a reflux condenser, after which the solvent was distilled off and the crude product (yellow oil) was analyzed by ^{1}H NMR.

If necessary, the desired chalcone **II** was precipitated from the oil with diethyl ether, filtered off, dried, and recrystallized from ethanol.

Ethyl 2-acetyl-3-(3-nitrophenyl)acrylate (chalcone IIa). *Z* Isomer. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.21 t [3H, C(O)CH$_2$C$\underline{H}_3$], 2.49 s (3H, CH$_3$), 4.28 q [2H, C(O)C$\underline{H}_2$CH$_3$], 7.99 s (H, −CH=), 7.80 t [H, C(5) Ar], 7.93 d [H, C(6) Ar], 8.32 dd [H, C(4) Ar], 8.40 s [H, C(2) Ar].

***E*-Isomer.** ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.29 t [3H, C(O)CH$_2$C$\underline{H}_3$], 2.40 s (3H, CH$_3$), 4.28 q [2H, C(O)C$\underline{H}_2$CH$_3$], 7.79 s (H, −CH=), 7.73 t [H, C(5) Ar], 7.88 d [H, C(6) Ar], 8.28 dd [H, C(4) Ar], 8.40 s [H, C(2) Ar]; mp 105–106°C. Found, %: C 59.11, H 4.97, N 5.29. $C_{13}H_{13}O_5N$. Calculated, %: C 59.32, H 4.94, N 5.32.

2,4-Bis(ethoxycarbonyl)-5-hydroxy-5-methyl-3-(3-nitrophenyl)cyclohexanone Va. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.86 t, 0.96 t [6H, 2C(O)CH$_2$C$\underline{H}_3$]; 1.30 s (3H, CH$_3$); 2.38 d, 2.97 d [2H, C(6), cyclohexanone]; 3.47 d [1H, C(4), cyclohexanone]; 3.83 m, 3.94 m [4H, 2C(O)C$\underline{H}_2$CH$_3$]; 4.01 t [1H, C(3), cyclohexanone]; 4.13 d [1H, C(2), cyclohexanone]; 5.02 s (1H, OH); 5.13 s [H, C(3)]; 7.60 t [H, C(5) Ar]; 7.77 d [H, C(6) Ar]; 8.21 dd [H, C(4) Ar]; 8.27 s [H, C(2) Ar]; mp 143–146°C. Found, %: C 58.05, H 5.85, N 3.56. $C_{17}H_{23}O_8N$. Calculated, %: C 58.01, H 5.85, N 3.56.

Ethyl 2-acetyl-3-(2,3-dichlorophenyl)acrylate (chalcone IIb). *Z* Isomer. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.06 t [3H, C(O)CH$_2$C$\underline{H}_3$], 2.47 s (3H, CH$_3$), 4.12 q [2H, C(O)C$\underline{H}_2$CH$_3$], 7.89 s (H, −CH=), 7.35 dd [H, C(6) Ar], 7.45 t [H, C(5) Ar], 7.73 dd [H, C(4) Ar].

***E*-Isomer.** ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.28 t [3H, C(O)CH$_2$C$\underline{H}_3$], 2.31 s (3H, CH$_3$), 4.29 q

[1] Samples were prepared at the Institute of Metal Physics, Ural Branch, Russian Academy of Sciences, laboratory headed by Prof. A.E. Ermakov.

[2H, C(O)C$\underline{H}_2$CH$_3$], 7.76 s (H, −CH=), 7.28 dd [H, C(6) Ar], 7.40 t [H, C(5) Ar], 7.73 dd [H, C(4) Ar]. Found, %: C 53.58, H 4.19. $C_{13}H_{12}O_3Cl_2$. Calculated, %: C 54.35, H 4.18.

2,4-Bis(ethoxycarbonyl)-5-hydroxy-5-methyl-3-(2,3-dichlorophenyl)cyclohexanone Vb. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.80 t, 0.93 t [6H, 2 C(O)CH$_2$C$\underline{H}_3$]; 1.25 s (3H, CH$_3$); 2.38 d, 2.81 d [2H, C(6), cyclohexanone]; 3.35 d [1H, C(4), cyclohexanone]; 3.82 m, 3.88 m [4H, C(O)C$\underline{H}_2$CH$_3$]; 4.03 d [1H, C(2), cyclohexanone]; 4.63 d [1H, C(3), cyclohexanone]; 5.02 s (1H, OH); 7.38 t [H, C(5) Ar]; 7.50 d [H, C(6) Ar]; 7.74 d [H, C(4) Ar]; mp 130–133°C. Found, %: C 54.50, H 5.18. $C_{17}H_{22}O_6Cl_2$. Calculated, %: C 54.67, H 5.27.

CONCLUSIONS

(1) Nanosized metal oxides are novel catalysts of the Knoevenagel reaction.

(2) Processes for preparing chalcones, intermediate products in the synthesis of Nitrendipine and Felodipine cardiotropic agents, were optimized.

(3) The results obtained can be used for optimizing the Knoevenagel reaction with other reactants.

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REFERENCES

1. Janis, R.A., Silver, P.J., and Triggle, D.J., *Adv. Drug Res*., 1987, vol. 16, p. 309.
2. UR Patent 5808084.
3. US Patent 5942624.
4. Lehnert, W., *Tetrahedron*, 1974, vol. 30, pp. 301–305.
5. Shanthan Rao, P. and Venkataratnam, R.V., *Tetrahedron Lett*., 1991, vol. 32, pp. 5821–5822.
6. Kantevari, S., Bantu, R., and Nagarapu, L., *J. Mol. Catal. A: Chem*., 2007, vol. 269, pp. 53–57.
7. Wang, Y., Shang, Z., Wu, T., et al., *J. Mol. Catal. A: Chem*., 2006, vol. 253, pp. 212–221.
8. Reddy, T.I. and Varma, R.S., *Tetrahedron Lett*., 1997, vol. 38, no. 10, pp. 1721–1724.
9. Dong, F., Li, Y., and Day, R., *Chin. Chem. Lett.,* 2007, vol. 18, pp. 266–268.
10. McNulty, J., Steere, J.A., and Wolf, S., *Tetrahedron Lett*., 1998, vol. 39, no. 44, pp. 8013–8016.
11. Kim, S.-Y., Kwon, P.-S., Kwon, T.-W., et al., *Synth. Commun.,* 1997, vol. 27, pp. 533–541.
12. Fedorova, O.V., Koryakova, O.V., Valova, M.S., et al., *Kinet. Katal*., 2010, vol. 51, no. 4, pp. 1–7.
13. Kharchuk, V.G., Koryakova, O.V., Khmara, E.F., and Uimin, M.A., *Anal. Kontrol'*, 2005, vol. 9, no. 4, pp. 423–427.