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Enantioselective Addition of Diethyl Malonate to ω-Nitrostyrenes in the Presence of Cobalt and Manganese Complexes with *N*,*N'*-Dibenzyl-(1*S*,2*S*)-cyclohexane-1,2-diamine

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Abstract—Enantioselective addition of diethyl malonate to nitrostyrene and *para*-chloronitrostyrene is catalyzed by cobalt and manganese complexes with *N*,*N'*-dibenzyl-(1*S*,2*S*)-cyclohexane-1,2-diamine generated *in situ*. Enantiomeric excess of the (*R*)-isomers in the reaction products is 66–87%.

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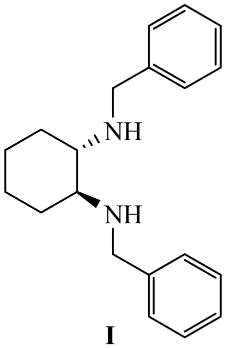
Enantioselective addition of diethyl malonate to ω-nitrostyrene is a convenient approach to the synthesis of key intermediates in producing neurotrophic agents (*R*)-phenotropil, (*R*)-phenibut, (*R*)-baclofen, and (*R*)-rolipram [1, 2]. Although at present these pharmaceuticals are produced in racemic form, it was found that the neurotropic activity is exhibited by the (*R*)-enantiomers, whereas the (*S*)-enantiomers are inactive [3].

The methods of synthesis of individual enantiomers described in the literature are based mainly on the separation of racemic mixtures of proper pharmaceutical substances or of their synthetic precursors [4–6]. A number of chemoenzymatic [7] and enantioselective syntheses of the (*R*)-phenibut and (*R*)-baclofen [8] preparations has been developed. However, these methods have several major drawbacks: low overall yields of desired products, the need for separation of the diastereomeric intermediates, the use of an expensive chiral auxiliary reagent in stoichiometric amount. Therefore it is still relevant to develop more cost-effective approaches to the synthesis of enantiomerically pure derivatives of γ-aminobutyric acid.

Since recently the methods became widespread of enantioselective organocatalysis for the enantioselective addition of various Michael donors to α,β-unsaturated nitro derivatives, which allowed obtaining high enantiomeric excesses in adducts [9]. However, the requirement of high concentrations of catalyst (5–20 mol %) and their synthetic inaccessibility limit the possibility of practical application of this method. It was shown [10] that the Ni(II) complexes with chiral ligands based on *trans*-(1*R*,2*R*)-cyclohexane-1,2-diamine are effective catalysts for the addition of some 1,3-dicarbonyl derivatives to nitroalkenes. The assumed mechanism involved the formation of the Ni(II) complex of acetylacetonate type, followed by intracoordination nucleophilic attack of the acetylacetonate ligand on the multiple bond of the nitroalkene. Evans et al. examined the effect of the nature of the 1,3-dicarbonyl compound and unsaturated substrate on the reaction rate and enantioselectivity. However, the scope of catalysts reviewed in [10] is limited to complexes of Ni(II) and there is no information on the impact of the metal nature on the catalytic properties of the metal complexes. The central role of the transition metal in the catalytic activation of 1,3-dicarbonyl compounds determines the interest in the study of its effect on the catalytic properties in the reactions of nitrostyrene with diethylmalonate.

We found that cobalt and manganese complexes with *N*,*N'*-dibenzyl-(1*S*,2*S*)-cyclohexane-1,2-diamine (**I**), generated in situ from the corresponding metal halide hydrates and the chiral diamine are enantioselective catalysts in the reaction of nitrostyrene **IIa** and *para*-chlornitrostyrene **IIb** with diethylmalonate **III**.



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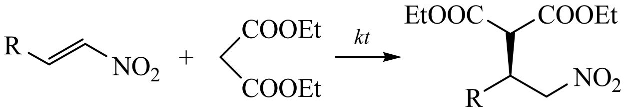

IIa, IIb **III** **IVa, IVb**

II, IVa: R = Ph; **II, IVb**: R = *p*-Cl-Ph.

The results of these studies are summarized in the table.

With the cobalt complex the enantiomeric excess of target (*R*)-nitroesters **IVa, IVb** reaches 87.0%, whereas the catalysis with manganese complex leads to (*R*)-(**IVa, IVb**) with the enantiomeric excess up to 79.0%.

The investigation of the effect of metal/ligand ratio on the catalytic properties of metal complexes obtained in situ (see the table) showed that among the cobalt complexes the maximum activity is reached at a ratio of 1/2, while further addition of ligand does not significantly change the catalyst properties. The complexes obtained with the ratio of metal/ligand = 1/1 proved to be inactive in the reaction.

The acido ligand nature affects significantly the catalytic properties of complexes. The manganese acetate complexes showed no catalytic activity. The catalytic activities and enantioselectivities of the cobalt chloride and bromide complexes in this reaction are similar.

Thus, the highest enantioselectivity in the addition reactions of diethylmalonate to nitrostyrene and *p*-chloronitrostyrene is achieved at the catalysis with the cobalt complexes; the use of the diamine (*S*,*S*)-isomer as a ligand leads to a product of (*R*)-configuration both in the case of complexes of cobalt and manganese.

EXPERIMENTAL

General procedure for the study of the reaction of α,β-unsaturated nitro derivatives (IIa, IIb) with diethylmalonate. All operations were performed in an argon atmosphere. To 0.432 mmol of *N*,*N'*-dibenzyl-(1*S*,2*S*)-cyclohexane-1,2-diamine **I** and 0.144 mmol of cobalt(II) chloride hexahydrate or manganese(II) chloride tetrahydrate was added 1.44 ml of diethyl malonate **III**, and the mixture was stirred until the formation of a homogeneous solution. The resulting 0.1 M of the catalyst solution in diethylmalonate (0.20 ml, 1.30 mmol of diethylmalonate) was added to a solution of 1 mmol of compound **IIa** or **IIb** in 3.75 ml of toluene. The reaction mixture was kept at a temperature of 20°C. The conversion (with respect to the nitro derivative **IIa, IIb**) was determined from ^{1}H NMR data. Compounds **IVa, IVb** were isolated by chromatography on silica gel Kieselgel 60 (0.063–0.100 mm, Merck), eluent chloroform.

Catalytic properties of the generated in situ cobalt and manganese complexes in the reaction of nitroalkenes **IIa, IIb** with diethyl malonate

Catalyst	[M]:L	Concentration of catalyst, mol %	Substrate	Reaction time, h	Conversion of nitroalkene,%	(*R*)-**IVa, IVb**, % *ee*
$CoCl_2·6H_2O$ + **I**	1:2	2	**IIa**	41	91.0	86.2
$CoCl_2·6H_2O$ + **I**	1:2	2	**IIb**	96	100	87.0
$CoCl_2·6H_2O$ + **I**	1:1	0.2	**IIa**	108	0	–
$CoCl_2·6H_2O$ + **I**	1:2	0.2	**IIa**	108	32.0	86.0
$CoCl_2·6H_2O$ + **I**	1:3	0.2	**IIa**	108	35.0	81.3
$CoBr_2$ + **I**	1:2	0.2	**IIa**	108	34.3	86.7
$MnCl_2·4H_2O$ + **I**	1:3	2	**IIa**	16	99.7	66.0
$MnCl_2·4H_2O$ + **I**	1:3	2	**IIb**	96	85.7	79.0
$Mn(OAc)_2$ + **I**	1:3	2	**IIb**	16	0	–

Diethyl (*R*)-(2-nitro-1-phenylethyl)malonate (IVa). Yield 90.3%, $[\alpha]_D^{30}$ –6.62° (*c* 0.015 g ml^{-1}, $CHCl_3$), ($[\alpha]_D^{30}$ –6.00°, *c* 1.0, $CHCl_3$, for a product with *ee* 93% according to [1]). The ^1H and ^{13}C NMR spectra correspond to the published data [1]. Mass spectrum, *m/z* ($I_{rel.}$): 309 $[M]^+$, 263 (12), 218 (12), 190 (13), 189 (100), 171 (58), 161 (56), 145 (30) , 133 (22), 131 (20), 117 (28), 115 (70), 105 (15), 104 (55), 103 (34), 91 (26), 78 (15), 77 (20) .

Diethyl (*R*)-[2-nitro-1-(4-chlorophenyl)ethyl]malonate (IVb). Yield 87.2%, $[\alpha]_D^{20}$ –7.45° (*c* 0.015 g ml^{-1}, $CHCl_3$) ($[\alpha]_D^{25}$ –8.56°, $CHCl_3$ for the product with *ee* > 99% according to [1]). The ^1H, ^{13}C NMR spectra of the product correspond to the published data [1]. Mass spectrum, *m/z* ($I_{rel.}$): 343 $[M]^+$, 297 (10), 252 (7), 225 (37), 223 (100), 205 (42), 195 (53), 179 (20) , 149 (22), 138 (58), 115 (75), 103 (24), 89 (7), 77 (15).

N,*N*'-Dibenzyl-(1*S*,2*S*)-cyclohexane-1,2-diamine (**I**) was synthesized according to the method [10].

Enantiomeric composition of the reaction products was determined by HPLC using a column with a chiral stationary phase Chiralcel AD. Conditions for the analysis of **IVa**: eluent hexane–isopropanol (95:5), flow rate 1.0 ml min^{-1}. Retention time of (*R*)-**IVa,** t_r = 18.5 min, (*S*)-**IVa,** t_r = 43.1 min. For **IVb:** eluent hexane–isopropanol (65:35), flow rate 1.0 ml min^{-1}. Retention time for (*R*)-**IVb** t_r = 10.8 min, (*S*)-**IVb** t_r = 26.9 min.

NMR spectra were recorded on a Jeol JNM-ECX400 instrument using solvent $CDCl_3$ [399.78 (^1H) and 100.53 MHz (^{13}C)]. Measurements were carried out without the use of a reference compound, with reference to the frequency of the signal of deuterated solvent.

The mass spectra of the synthesized compounds were obtained on a gas chromatograph-mass spectrometer Finnigan Trace DCQ using a capillary column SGE BPX-5 30×0.32 mm at the energy of ionizing electrons 70 eV.

Determination of the specific rotation angles was carried out on a Rudolph Research Analytical polarimeter.

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