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Modified Hantzsch Reaction in the Presence of Chiral Organic Catalysts

A. M. Magerramov[a], E. Z. Guseinov[a], I. M. Akhmedov[a], Dj. Tanyeli[b], and M. M. Kurbanova[a]*

[a] *Baku State University, ul. Z. Khalilova 23, Baku, AZ-1073, Azerbaidjan*
**e-mail: kurbanova1972@rambler.ru*
[b] *Middle East Technical University, Ankara, Turkey*

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Abstract—Modified Hantzsch reaction in three- and four-component system in the presence of new chiral organic catalysts was investigated and the advantages of this reaction in three-component system compared to four-component one were demonstrated, the influence of catalysts on the dynamics and stereochemistry of the reaction was elucidated. The enantiomeric excess of the main reaction product was evaluated with HPLC, its structure was proved by X-ray diffraction analysis.

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Hantzsch reaction, discovered in nineteenth century, in the present time has not lost its practical value. By this reaction nowadays dozens of derivatives of 1,4-dihydropyridines are synthesized (amlodipine, nifedipine, nimodipine, felodipine, nicardipine, and nitrendipine) used in treating a number of diseases [1, 2].

Considering these facts, most of researchers apply modified methods of Hantzsch reaction using various catalysts. As examples the syntheses may be cited in a microwave oven, using the solar energy, and ultra sound signals, in aqueous environment or in ionic liquids, in the presence of Lewis catalysts, etc. [3–6]. The goal of all methods is the preparation of the product of high purity and the reduction of the reaction duration.

A classic method of synthesis of biologically vital hexahydroqinolines is a three-component condensation of aldehyde, acetoacetic ester, and ammonium acetate in anhydrous ethanol [7]. The drawback of this method along with a high expenditure of solvent and a significant reaction time is the low yield of the condensation product. As an example of contemporary methods may be regarded a reaction without solvent or in a ionic liquid. Then the reaction will correspond to green chemistry principals [8–10].

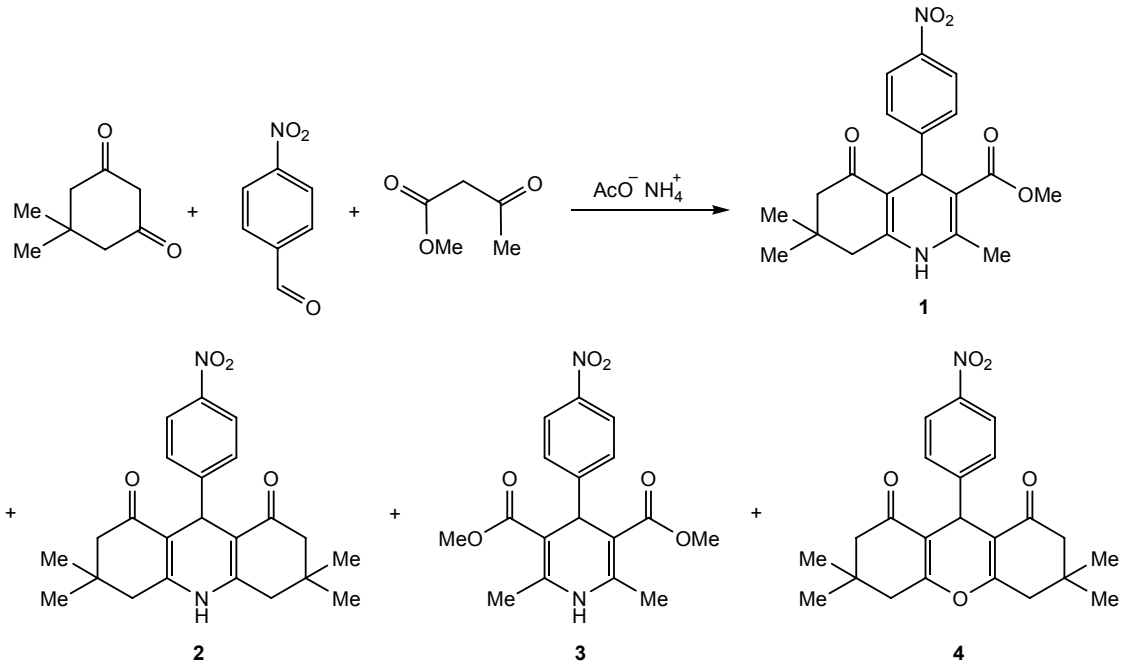
It is known that the final product of Hantzsch reaction forms at the condensation of intermediate product of the reaction of methylene-active compound with ammonia [11]. The diversity of the intermediate products in the four-component reaction leads to the reaction proceeding in several different directions. This study consists in a parallel comparative study of Hantzsch reaction in three- and four-component systems.

In the reaction along with the main product **1** secondary products **2**–**4** are generated (Schemes 1, 2). Compounds **2** and **3** are formed from one of the methylene-active compounds participating in the condensation, and the xanthene derivative **4** is due to the involvement in cyclization of dimedone and enamine. The yield of compound **4** reduces at 20–25% excess of ammonium acetate. The above facts lead to decreasing the practical yield of ester **1**. At introducing in the reaction the preliminary prepared enamine, namely, at the transition from the four-component Hantzsch reaction to three-component system the number of side reactions and the yields of side products decrease.

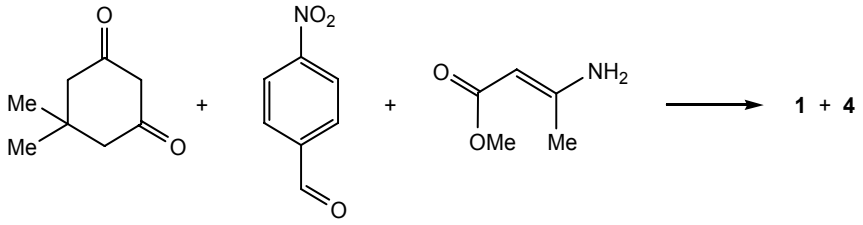
At performing the reaction by Scheme 2 the formation of compounds **2** and **3** is not observed, and compound **4** is formed in relatively lower amount compared to Scheme 1.

The generation of side products may be related not only to initial compounds, but also to the solvent. For

Scheme 1.



Scheme 2.



example, in the reaction carried out by Schemes 1 and 2 in ethanol hemiacetal and acetal are formed, the products of the solvent reaction with the initial aldehyde. This leads to a reduced yield of the target product. To prevent this undesirable effect the reaction is performed in dichlormethane, not in ethanol.

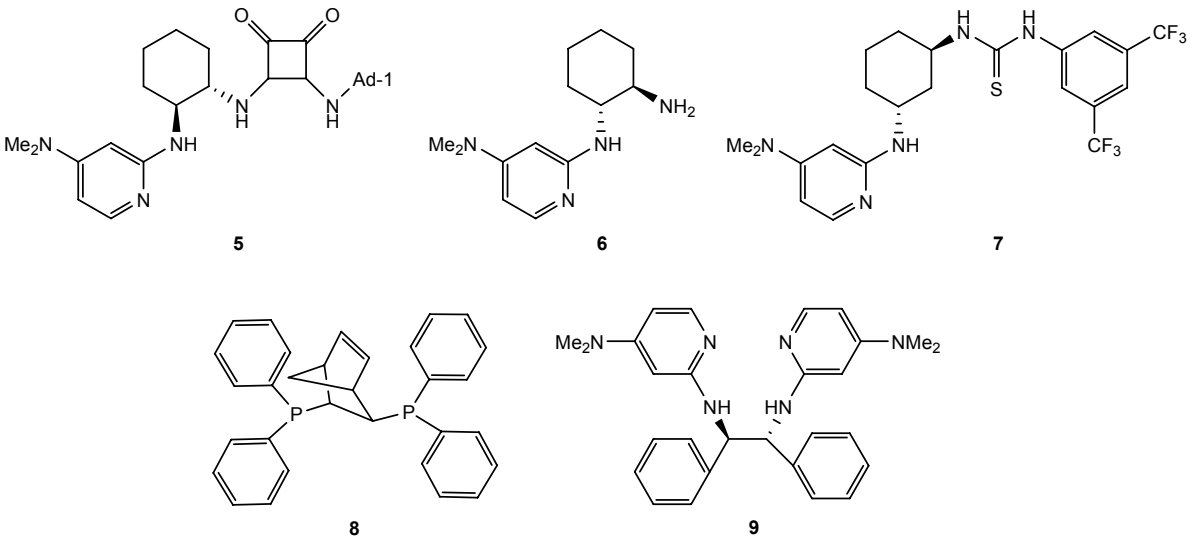


Table 1. Yields of products of Hantzsch reaction (%) involving *p*-nitrobenzaldehyde, methyl acetoacetate, dimedone, and ammonium acetate

Catalyst no.	Four-component system (scheme 1)				Three-component system (scheme 2)	
	1	**2**	**3**	**4**	**1**	**4**
5	67	11	7	5	87	5
6	70	10	8	4	90	4
7	72	8	6	4	91	3
8	64	4	5	3	86	3
9	69	9	7	4	89	4

Enamine used in the three-component Hantzsch reaction was synthesized by method [12].

In our investigations we used chiral organic catalysts **5–9** synthesized for Michael and Henry reactions; in two-component systems they affect both the optical purity of the reaction product and the process kinetics [13–15]. Since Hantzsch reaction proceeds in a multicomponent system, the above catalysts cannot show a high enantioselectivity, but can effectively influence the reaction kinetics. Our study showed that in the presence of catalysts **5–9** Hantzsch reaction proceeded 2–5 times faster than with the other catalysts.

Preparative yields of the main and side reaction products, obtained by Schemes 1 and 2, and the degree of enantiomeric excess of the principal product **1** are demonstrated in Tables 1 and 2.

The structure of the principal product **1** is confirmed by X-ray diffraction (XRD) analysis (Fig. 1). Compound **1** is a diastereomer with one asymmetric center at the atom C^1. The crystal of the studied compound is formed of a racemate with the relative configuration of the chiral atom *rac*-1*R**. Atoms O^4 and O^5 of the nitro group are disordered by two positions in a ratio 75 : 25.

In the crystal enantiomers form zigzag chain bound with intermolecular hydrogen bonds N^1–H···O^1 (–*x* + 1/2, –*y* + 1/2, *z* – 1/2) [N···O 2.887(2), H···O 1.99 Å, angle NHO 177°] (Fig. 2).

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker AV-400 (400 and 100 MHz respectively), internal reference TMS. Reaction products were isolated by column chromatography on silica gel (Merck, 0.2 mm). The reaction course and the purity of obtained compounds were monitored by TLC on Silufol UV-254 plates, eluent ethyl acetate–hexane, 1 : 8, development under UV irradiation. Elemental analysis was carried out on CHNO-analyzer Perkin Elmer 2400. The degree of enantiomeric excess (*ee*) was measured by HPLC using chiral columns Daicell AD-H (0.46 × 25 cm).

The single crystal of compound **1** for XRD analysis was obtained by a double recrystallizing from ethanol. XRD analysis was performed on a diffractometer Bruker Smart Apex II CCD (296 K, λMoK_α-radiation, graphite monochromator, φ- and ω-scanning, $2\theta_{max}$ 54°). Yellow crystal ($C_{20}H_{22}N_2O_5$, M_r 370.40), mp 232–234°C, size 0.30 × 0.20 × 0.20 mm, tetragonal: *a* 16.298(10), *b* 16.298(10), *c* 14.2530(9) Å, *V* 3786.0(4) Å^3, space group P-421s, *Z* 8, d_x 1.300 g/cm^3, μ 0.094 mm^{-1}.

Intensities of 47334 reflections (4095 independent, R_{int} 0.0214) were measured, the semiempirical correction for extinction was introduced by program SADABS [16].

Table 2. Enantiomeric characteristics of Hantzsch reaction product **1** obtained in the presence of chiral catalysts **5–9**

Catalyst no.	Enantiomers ratio *er*	Enantiomeric excess *ee*, %
5	52:48	4
6	52:48	4
7	54:46	8
8	54:46	8
9	55:45	10

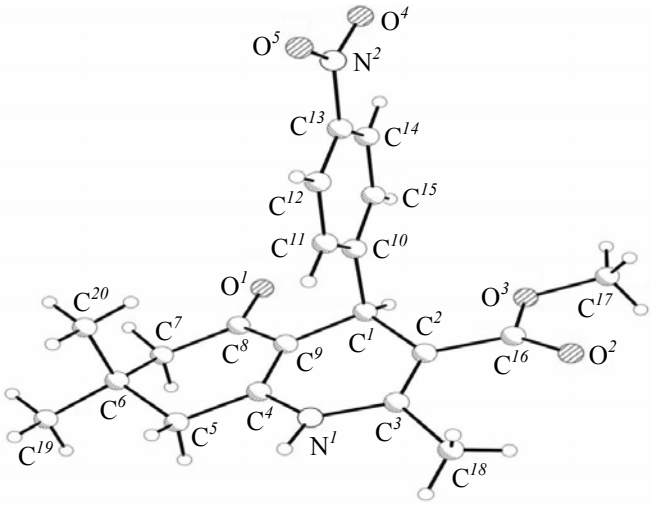


Fig. 1. Molecular structure of methyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-car-

The structure of compound **1** was solved by the direct method and refined by the least-squares method in anisotropic approximation for nonhydrogen atoms. Hydrogen atom of amino group was revealed objectively in the differential Fourier synthesis and was included in refinement with fixed positional and thermal [U_{iso} (H) = 1.2 U_{eq} (N)] parameters. Coordinates of the other hydrogen atoms were calculated geometrically and refined by the *rider* model with thermal parameters U_{eq} (H) = 1.5U_{eq} (C) for CH_3 groups and U_{eq} (H) = 1.2 U_{eq} (C) for all other groups. Terminal values of divergence factors R_1 0.043 for 3744 independent reflections with $I > 2\sigma(I)$, wR_2 0.1016 for all independent reflections. All calculations were made by software package SHELXTL [17].

The crystallographic data of structure **1** are deposited in Cambridge Crystallographic Data Center (under the number CCDC 1019892).

Four-component reaction (Scheme 1). To a mixture of 0.014 g (0.1 mol) of dimedone, 0.01 mL (0.1 mol) of methyl acetoacetate, 0.015 g (0.1 mol) of *p*-nitrobenzaldehyde, and 0.096 g (0.125 mmol) of ammonium acetate at room temperature was added 1 mL of methylene chloride and 5 mmol of catalyst **5–9**, the mixture was stirred for 1 h, then the solution was evaporated on a rotary evaporator. From the residue the reaction products were isolated by column chromatography, eluent ethyl acetate–hexane, 1 : 8. Compounds were eluted in the following order: **4**, **2**, **3**, and **1**. Yield of compound **1** 64–72%.

Three-component reaction (Scheme 2) was performed in a similar way. From 0.014 g (0.1 mol) of dimedone, 0.015 g (0.1 mol) of *p*-nitrobenzaldehyde and 0.0148 g (0.1 mol) of enamine compound **1** was obtained in 86–91% yield.

Methyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.86–1.05 s (6H, $2CH_3$), 2.16–2.55 d.d.d.d (4H, $2CH_2$, *J* 17.0, 17.4, 17.6, 17.6 Hz), 2.43 s (3H, CH_3), 3.56 s (3H, CH_3), 5.03 s (1H, CH), 7.41–8.14 d.d (4H, Ph, *J* 8.8, 8.8 Hz), 9.32 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 18.19 (CH_3), 26.05 (CH_3), 28.96 (CH_3), 32.19 (C), 36.47 (CH_2), 38.75 (CH), 50.20 (CH_2), 50.88

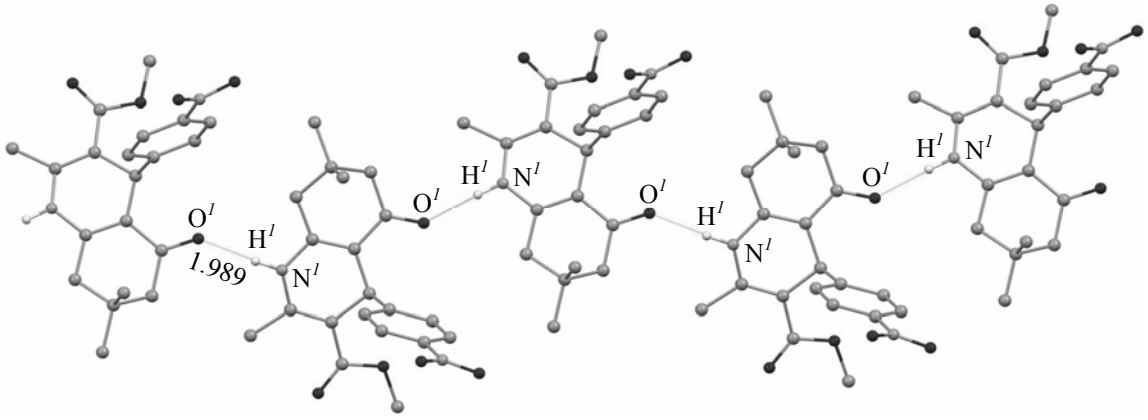


Fig. 2. Zigzag chains of molecules of methyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate **1** bound with intermolecular hydrogen bonds, according to XRD analysis data.

(OCH_3), 102.06 (C), 108.94 (C), 123.03 (2Ph), 128.90 (2Ph), 145.54 (CNO_2), 145.87 (CPh), 150.46 (2C), 155.05 (CPh), 167.09 (COO), 194.52 (CO). Found, %: C 64.81; H 5.90; N 7.54. $C_{20}H_{22}N_2O_5$. Calculated, %: C 64.86; H 5.94; N 7.56.

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.98–1.09 s (12H, $4CH_3$), 2.15–2.44 d.d.d.d (8H, $4CH_2$, *J* 16.8, 17.2, 18.0, 18.0 Hz), 5.47 s (1H, CH), 7.11–8.05 d.d (4H, Ph, *J* 8.4, 8.4 Hz), 11.73 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 25.45 ($2CH_3$), 27.16 ($2CH_3$), 29.39 (2C), 31.35 (CH), 44.78 ($2CH_2$), 45.08 ($2CH_2$), 112.71 (2C), 121.82 (2Ph), 122.13 (2Ph), 125.45 (CNO_2), 144.04 (2C), 144.73 (CPh), 187.50 (2CO). Found, %: C 70.09; H 6.63; N 7.16. $C_{23}H_{26}N_2O_4$. Calculated, %: C 70.05; H 6.59; N 7.10.

Dimethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.29 s (6H, $2CH_3$), 3.57 s (3H, CH_3), 5.03 s (1H, CH), 5.83 s (1H, NH), 7.35–8.02 d.d (4H, Ph, *J* 8.7, 8.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.60 ($2CH_3$), 38.91 (CH), 50.00 ($2OCH_3$), 101.95 (2C), 122.50 (2CHPh), 127.12 (2CHPh), 143.38 (2CNH), 145.33 (CNO_2), 153.16 (CPh), 166.57 (2CO). Found, %: C 58.99; H 5.27; N 8.13. $C_{17}H_{18}N_2O_6$. Calculated, %: C 58.96; H 5.20; N 8.09.

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (4). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.05–1.17 s (12H, $4CH_3$), 2.17–2.40 d.d.d.d (4H, $2CH_2$, *J* 16.9, 17.3, 17.9, 17.9 Hz), 5.44 s (1H, CH), 7.19–8.08 d.d (4H, Ph, *J* 8.8, 8.8 Hz). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 24.81 ($2CH_3$), 27.16 ($2CH_3$), 29.11 (2C), 30.70 (CH), 43.49 ($2CH_2$), 44.47 ($2CH_2$), 112.04 (2C), 121.82 (2Ph), 122.49 (2Ph), 125.13 (CNO_2), 144.33 (CPh), 145.03 (2C), 186.52 (CO). Found, %: C 69.91; H 6.41; N 3.58. $C_{23}H_{25}NO_5$. Calculated, %: C 69.87; H 6.32; N 3.54.

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