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THE SYNTHESIS OF OPTICALLY ACTIVE METHYL 2,7,7-TRIMETHYL-5-OXO-4- (4-METHOXYPHENYL) -1,4,5,6,7,8-HEXAHYDROXYNOLIN-3-CARBOXYLATE BASED ON MODIFIED HANS REACTION

Abstract: *On the basis modified Hans reaction and with the presence of various catalysts has been synthesized optically active methyl 2,7,7-trimethyl-5-oxo-4- (4-methoxyphenyl) -1,4,5,6,7,8-hexahydroxinoline-3- carboxylate. The degree of optical purity of the synthesized compound was studied by HPLC analysis. Factors influencing to the practical output of the reaction and the degree of optical purity of the synthesized compound were studied in comparative form in two- and three-component reactions.*

Key words: *Assimetric Hans reaction, chiral catalyst, optical purity degree.*

Language: *English*

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Introduction

The Hans reaction is the most important reaction for the synthesis of pyridine derivatives. Synthesis of pyridine derivatives always is one of the demand areas in the organic synthesis. Most derivatives of 1,4-dihydropyridine synthesized on the basis of Hans reaction are considered to be highly important compounds in medicine. The products of this reaction are the most widely used substances in pharmaceuticals over the past 20 years.

Lerkanidipine- a derivative of the 4-substituted 1,4 dihydropyride to regulate the activity of the blood vessel function and to provide more efficient cardiac function [1], kilnidipine in the treatment of

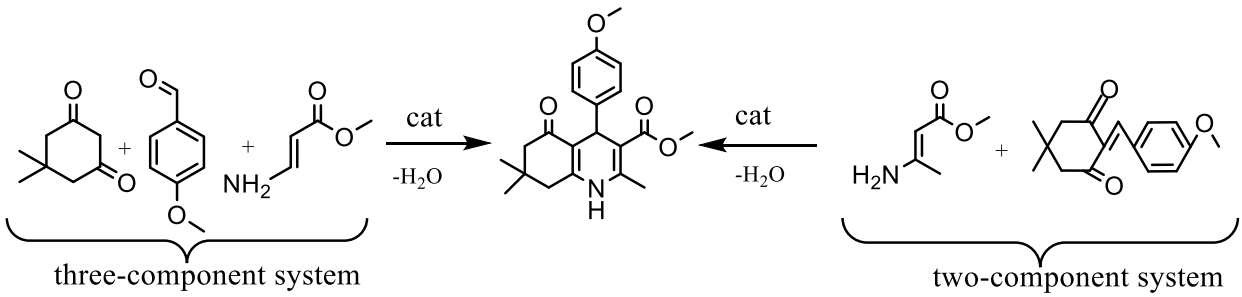
hypertension [2], Barnidipin- to reduce blood pressure and normalize blood flow to the kidneys [3],Lacidipine, manidipine and nisoldipine preparates which is included to the calcium channel blockers-normalizing blood pressure [4], Nilvadipine - in the treatment of cerebral artery seizures and Alzheimer's disease [5], Isradipine-in reducing the risk of stroke and heart attack and in the treatment of high blood pressure [6], Nifedipine in the treatment of cancer and tetanus, food pneumonia, lung and ischemic diseases, myocardial infarction [7], Nicardipine-in the angina, hypertension, vascular disease, heart failure [8], amlodipine-in chronic angina, stimulation of heart muscle, high blood pressure treatment [9], Nimodipine-is used for cerebral injury (cerebral hemorrhage) and in the treatment of high blood pressure [10].

As the derivatives of dihydropyridine have such a wide range of applications, the development and study of new methods for their synthesis is currently relevant. There is enough work in literature devoted to these issues. Currently, many new methods are being developed for this reaction. Large-scale studies have been carried out using various catalysts, environmentally friendly methods, and different reaction conditions to improve the Hans reaction. These studies include synthesis in microwave ovens [11], synthesis by solar energy and ultraviolet signals [12], synthesis in ionic liquids and aquatic environments [13], synthesis by Lewis catalysts [14] and so on. In all areas of research, the mainly focus is directed to obtaining high purity and output, reducing the reaction time, and at the same time anticipating the principles of green chemistry. In recent years, it is preferable that these reactions occur without solvent involvement [15]. Conducting the reaction in these conditions, along with its efficiency, also provides environmental harm.

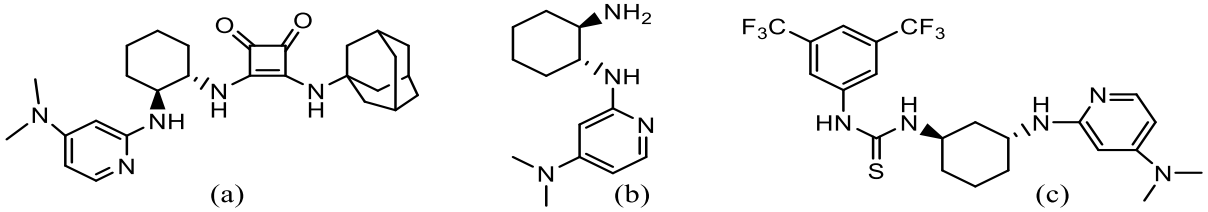
Result and discussion

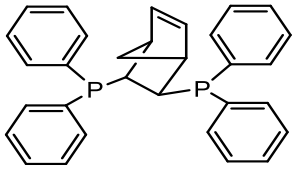
The presented research work is directed to increasing practical and optical output by modifying the Hans reaction.

From the mechanism of the classic Hans reaction is known that during the reaction of methylenactive compound (as an intermediate product)- with aldehyde obtained Knevenagel adduct but from the reaction with ammonia is obtained enamin. Condensation of this additive and enamel results in the final product acquisition [16, 17]. When using a methylenactive compound during the reaction, a symmetric product is obtained.Two different methylenactive compounds are used for asymmetric synthesis. The presence of two different methylenactive compounds in the environment causes additional intermediate products, which, along with asymmetric products, result in the formation of undesirable symmetric products. This reduces the degree of optical purity and practical output of the product.



During the reaction.were used following crystal organic catalysts [18].





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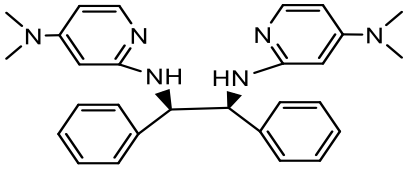

(e)

During the two- and three-component condensation, depending on the catalyst used the practical yield of the reaction and the optical purity of the product are given in the following table.

catalyst	Yield(%)			
	three-component		two-component	
	practical	ee	practical	ee
a	86	26	91	46
b	87	22	93	34
c	90	27	95	38
d	91	14	96	28
e	85	19	90	36

The pactical yield and the optical purity of the product of the reaction during two- and three-component condensation depending on the catalyst used are given in the following table. As it can be seen, both the practical yield and the optical purity rate in the two-component reaction are higher than the three-component reaction. In the four-component classical Hans reaction, the parameters mentioned are lower.

Experimental

Melting points are uncorrected and were recorded on SMP 30 apparatus. 1H NMR and 13C NMR spectra ware recorded on a 400 spectrophotometr using in DMSO-d6 as the solvent. Chemical shifts values are reported in ppm taking tetramethylsilane as the internal standart and J values are given in hertz. The types of signals are indicated by the following letters: s=singlet, d=doublet, t=triplet, m=multiplet. Polarimetric measurements were made by AUTOPOL III automatic polarimetr and reported as follows: [α] *T D* (c in g per 100 ml, solvent). Enantiomeric excess (ee) values of chiral adducts were measured by an HPLC system using a AS-H chiral column (0.46 cm × 25 cm) and AD-H chiral column (0.46 cm × 25 cm). Flash column chromotography (FCC) was performed by using glass columns with flash grade silica gel (70-230 mesh). Reactions were monitored by thinlayer chromotography (TLC) using precoated silica gel plates, visualized by UV light. All organic extracts were dehydrated over oven-dried MgSO4

To the 10 ml small reaction tube (a, b, c, d, e) were added 0.121 ml (1 mmol) 4-methoxybenzaldehyde, 0.14 g (1 mmol) dimedone, 0.115 g (1 mmol) methyl 3-amino-crotonate, 1 ml dichlormethane and 5 mmol% catalyst. The mixture was stirred with the magnetic mixer at room temperature for 1-22 hours depending on the catalyst. The progress of reaction was monitored by TLC. After the completion of reaction, the product of reaction purified by chromatography eluting with ethyl acetate and hexane (1:6, MerckSilica Gel 60 F254, 0,070-0.230 mm). Depending on the catalysts, the actual yield of the product was 86, 87, 90, 91 and 85%, respectively. The synthesized methyl 2,7,7-trimethyl-5-oxo-4- (4-methoxyphenyl) -1.4,5,6,7,8-hexahydroxinoline-3-carboxylated is yellow color solid compound. $T_{m.p.}$=256 ºC

For the synthesis of the same substance with two-component condensation were added 0.258 g (1 mmol) 5,5-dimethyl-2- (4-methoxybenzylene) cyclohexane-1,3-dion and 0.115 g (1 mmol) methyl 3-aminotrotonate, 1 ml of dihlormethane for synthesis 5 mmol% crystal-organic catalysts (a, b, c, d, e). The mixture was stirred at room temperature 0.5-2 h depending on the catalyst. After the completion of reaction, the

product of reaction purified by chromatography. Depending on the catalysts, the actual yield of the product was 91, 93, 95, 97 and 90%, respectively.

^{1}H NMR (400MHz, DMSO-d_6): 0.95 (s, 3H, CH3), 1.17 (s, 3H, CH3), 2.15-2.23 (dd, 2H, J = 12.2 ,J=12.7, CH2), 2.33-2.41 (dd, 2H, J =12.9, J=15.2 CH2), 2.39 (s, 3H, CH3), 3.64 (s, 3H, OCH3), 5.08 (s, 1H, CH), 7.15-7.26 (dd, 4H, J=7.3,J=7.7,Ar),8.03(s,1H,NH).

^{13}C NMR(100MHz, DMSO-d_6): 19.47, 26.96, 28.74, 32.81, 36.04, 40.98, 41.04, 41.95, 42.09, 43.06, 52.81, 105.87, 112.14, 126.18, 128.96, 130.916, 144.71, 147.16, 151.36, 168.23, 196.15.

References:

1. Barrios, V., et al. (2006). "Lercanidipine is an effective and well tolerated antihypertensive drug regardless the cardiovascular risk profile: The LAURA study". *International journal of clinical practice*, V, 60 (11), pp. 1364–70.
2. Löhn, M., et al. (2002). "Cilnidipine is a novel slow-acting blocker of vascular L-type calcium channels that does not target protein kinase C". J. Hypertens, V, 20 (5), pp. 885–93.
3. Geneeskd, N.T., Elisabeth, S., Ziekenhuis, B. (1997). a Novel Calcium Antagonist for Once-Daily Treatment of Hypertension: A Multicenter, Double-Blind, Placebo-Controlled, Dose-Ranging Study. *Cardiovascular Drugs and Therapy*, V, 11(5), pp. 637-643.
4. Otero, M.L. (2007). "Manidipine–delapril combination in the management of hyper-tension". *Vascular Health and Risk Management*, V, 3 (3), pp.255–63.
5. Pattan, S.R., Parate, A.N., Sirisha, K., Achaiah, G., & Reddy, V.M. (2007). Chemical and Pharmacological significance of 1,4-dihydropyridines- A Review. *Indian Drugs*, V, 44(2), pp. 73-90.
6. Ganz, M., Mokabberi, R., & Sica, D. (2005). "Comparison of blood pressure control with amlodipine and controlled-release isradipine: an open-label, drug substitution study". *J Clin Hypertens (Greenwich)*, V, 7, pp. 27–31.
7. Hayashi, K., et al. (2006). "T-type Ca channel blockade as a determinant of kidney protection". *Keio J Med*, V, 59 (3), pp. 84-95.
8. Huang, R.I, et al. (2006). "Efficacy of intracoronary nicardipine in the treatment of no-reflow during percutaneous coronary intervention". *Catheter Cardiovasc Interv*, V, 68 (5), pp. 671–676.
9. Cooper, K., Fray, M.J., Parry, M.J., Richardson, K., & Steele, J. (1992). 1,4-Dihydropyridines as antagonists of platelet activating factor. Synthesis and structure-activity relationships of 2-(4-heterocyclyl)phenyl derivatives. *J Med Chem*., V, 17, pp. 3115-3129.
10. Belfort, M.A., Anthony, J., Saade, G.R., & Allen, J.C. (2003). "A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia". *N. Engl. J. Med*, V, 348 (4), pp. 304–311.
11. Kidwai, M., Saxena, S., Mohan, R., & Venkataramanan, R. (2002). A novel *one* pot synthesis ofnitrogen containing heterocycles: an alternate methodology to the Biginelli and Hantzsch reactions. *J. Chem. Soc. Perkin Trans*, V, 1, pp. 1845-1846.
12. Legeay, J., Eyndeb, J.V., & Bazureau, J.P. (2005). Hantzsch 1,4-dihydropyridine synthesis in aqueous ethanol by visible light**.** *Tetrahedron*, V, 61, pp. 12386–12397.
13. Ohberg, L., & Westman, J. (2002). An Efficient and Fast Procedure for the syntesis of Hantzsch 1,4-dihydropyridines under Microwave Conditions. *Synlett*, V, 8, pp. 1296-1298.
14. Yadav, J.S., Reddy, B.V.S., Basak, A. K., & Narsaiah, A.V. (2003). Three-component coupling reactions in ionic liquids: an improved protocol for the synthesis of 1,4-dihydropyridines. *Green Chem*., V, 5, pp. 60–63.
15. Wen, L., Ji, C., Li, Y., & Li, M. (20009). Solvent-free and efficient synthesis of polyhydroquinoline derivatives, *Comb. Chem*, V, 11, pp. 799–805.
16. Maharramov, A.M., Ahmadov, İ.M., Kurbanova, M.M., Huseynov, E.Z., & Tanyeli, J. (2013). Synthesis of optically active methyl 2,7,7-trimethyl-5-oxo-4-(4- nitro) phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate. *Baku University News*, №4, pp. 23-30.
17. Magerramov, A. M., Guseinov, E. Z., Akhmedov, İ. M., Tanyeli, D., & Kurbanova,

M.M. (n.d.). Modified Hantzsch reaction in the presence of chiral organic catalysts. *Russian Journal of Organic Chemistry*, 52 (5), 701-705.

18. Emre, Y. Y., & Cihangir, T. (2012). A method for the synthesis of pyridine-based C2-symmetrical chiral nucleophilic organocatalysts via Pd-catalyzed coupling. *Tetrahedron: Asymmetry.*, 23, pp.1694–1699.