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-hexahydroxynolin-3-carboxylate. The degree of optical purity of the synthesized compound was studied by HPLC analysis. Factors influencing 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 dihydropyridine to regulate the activity of the blood vessel function and to provide more efficient cardiac function [1], kilnidipine in the treatment of...
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hypothesis [2], Barnidipin - to reduce blood pressure and normalize blood flow to the kidneys [3], Lacidipine, manidipine and nisoldipine prepartes 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 enam. 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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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 practical 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 were recorded on a 400 spectrophotometr using in DMSO-d6 as the solvent. Chemical shifts values are reported in ppm taking tetramethylsilane as the internal standard 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 polarimeter 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 chromatography (FCC) was performed by using glass columns with flash grade silica gel (70-230 mesh). Reactions were monitored by thinlayer chromatography (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) dinedone, 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-hexahydroxinoine-3-carboxylated is yellow color solid compound. Tm,p=256 °C.

For the synthesis of the same substance with two-component condensation were added 0.258 g (1 mmol) 5,5-dimethyl-2-(4-methoxybenzylen) 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
1H NMR (400MHz, DMSO-d6): 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).

13C NMR(100MHz, DMSO-d6): 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, 160.23, 196.15.

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