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SYNTHESIS OF DIHYDROPYRIMIDINE DERIVATIVES BY BIGINELLI'S REACTION IN STUDENT WORKSHOPS ON ORGANIC CHEMISTRY

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Abstract. In classical student workshops, the attention paid to the synthesis of heterocyclic compounds is very little. This is due to the complexity and duration of most of these syntheses, the low availability of the initial reagents, the difficult isolation and purification the reaction products. Biginelli's reaction, as a method of synthesis of dihydropyrimidones, is attractive to be used in the student workshop on chemistry due to the simple procedure of synthesis, as well as a possibility to vary the reaction conditions and select initial reagents to introduce substituents that may be easily transformed to various functional groups. All of the above allows forming creative approach to the work performing and independent thinking in students, their ability to self-education and self-development. Students cannot only get acquainted with the basic experimental methods, but also learn how to apply theoretical knowledge in practice, including monitoring of reactions and analyzing organic compounds by physico-chemical methods.

Keywords: dihydropyrimidone, student workshop, Biginelly reaction, multiple-component reaction, heterocycle

Introduction. One of the urgent problems of modern organic chemistry consists in creation of complex heterocyclic compounds from simple substrates. An important role to solve this problem is played by multiple-component reactions that are widely used in practice. One of them is the synthesis of 3,4-dihydropyrimidine derivatives by the reaction developed by the Italian chemist Pietro Biginelli in 1893.

The essence of this method is the interaction between ethyl acetoacetate, an aryl aldehyde (such as benzaldehyde) and urea catalyzed by Bronsted or Lewis acids according to the scheme:

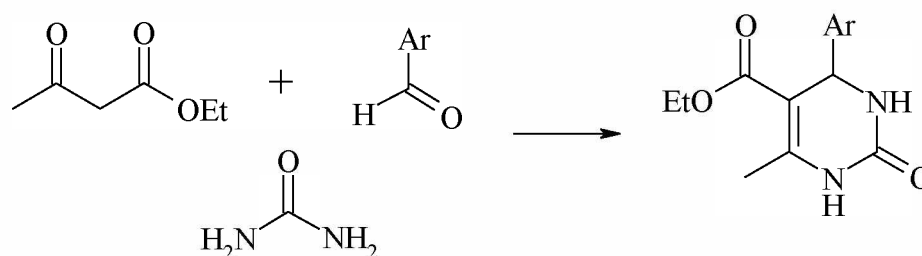


Fig. 1.

For almost 100 years, this method of synthesis of dihydropyrimidones has been undeservedly forgotten. However, recently dihydropyrimidones have attracted the attention of chemists and pharmacologists again due to their high and diverse biological activity - analgesic, antibacterial, antihypertensive [1] etc. Dihydropyrimidones are widely used in the pharmaceutical industry as calcium channel blockers [11] and antihypertensive agents.

According to the classical procedure, Biginelli's reaction occurs under the conditions of long-term boiling of the reagents (10-15 hours) in ethanol medium in the presence of 20 % HCl to form substituted dihydropyrimidones in low yields that make this method inconvenient. Furthermore, the isolation of the end dihydropyrimidones is complicated by the formation of a significant amount of by-products. That is why many articles are devoted to changing the reaction conditions in order to improve the yield of dihydropyrimidones [2], and their number increases every year [2,3].

Results and discussion. One of the approaches to modifying reaction conditions is the changing of solvents (acetic acid, acetonitrile, THF, DMFA etc.) and various catalytic systems (organic and inorganic acids, Lewis acids, ionic liquids). To speed up the reaction rate, microwave and infrared radiation or ultrasound are used, that allows reducing the reaction time to several minutes and increasing the end product yield to 98 % [4]. In this case, due to the high selectivity of the process, it is not necessary to further purify the reaction products by recrystallization or chromatography. It should be noted, when unsymmetrical dicarbonyl compounds are used, the reaction always proceeds regioselectively.

In classical student workshops, the attention paid to the synthesis of heterocyclic compounds is very little. This is due to the complexity and duration of most of these synthesis, the low availability of the initial reagents, the difficult isolation and purification the reaction products. The simple procedure of synthesis, as well as a possibility to vary the reaction conditions and select initial reagents to introduce substituents that may be easily transformed to various functional groups, make Biginelli's reaction attractive to be used in the student workshop on chemistry. All of the above corresponds to the aims of the student workshop on chemistry to form creative approach to the work performing and independent thinking in students and their ability to self-education and self-development. After all, students should not only get acquainted with the basic experimental methods, but also learn how to apply theoretical knowledge in practice, including monitoring of reactions and analyzing organic compounds by physico-chemical methods. Thus, due to the procedure simplicity, the high selectivity and the simplicity of the isolation of the end products, the synthesis of dihydropyrimidines by this method is a convenient model reaction for the student workshop on chemistry of heterocyclic compounds, in particular, when methods for obtaining compounds with a pyrimidine nucleus are studied

Our main aim was to modify the Biginelli's reaction, taking into account the aims of the student workshop and the laboratory sessions duration, by selection of solvents, starting reagents and catalysts to achieve:

- 1) decreasing the reaction time;
- 2) simplifiety the isolation procedure of reaction products and their identification.

We improved the method reported in [5], that made it possible to carry out the synthesis under mild conditions, in particular, by refluxing the reagents - acetoacetic ether, aromatic aldehyde and urea or thiourea in acetic acid media in the presence of Lewis acids for 1-2 hours. To be used as starting reagents, the aromatic aldehydes, for example, 4-CH₃OC₆H₅, 4-CH₃C₆H₅, containing substituents that are well identified by nuclear magnetic resonance (NMR) spectroscopy are offered.

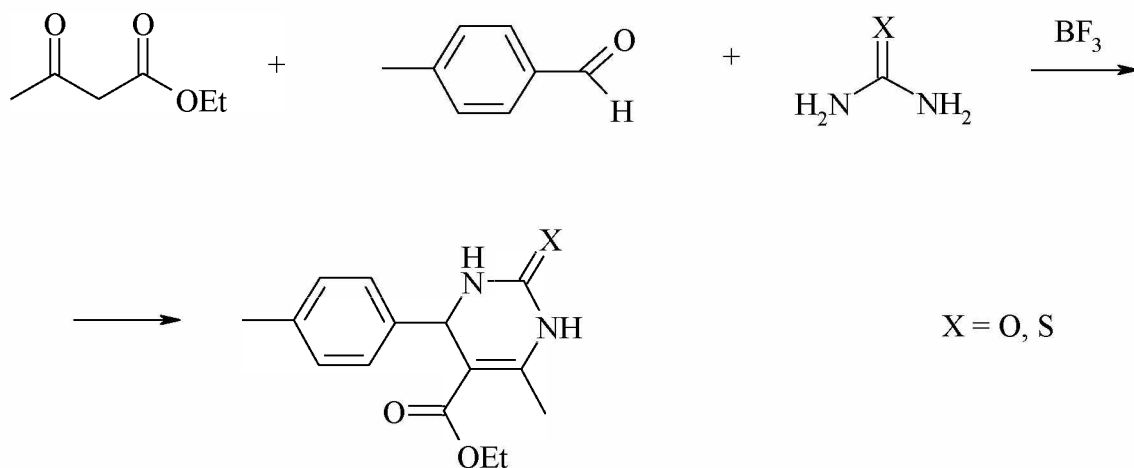


Fig. 2.

Since in the NMR ¹H spectra the initial and final compounds are characterized by well expressed signals and their chemical shifts are significantly different in position, NMR ¹H spectroscopy can be used not only for the identification of reaction products, but also for kinetic studies in the physical chemistry course.

The advantages of the offered method are:

- 1) a simple procedure of synthesis,
- 2) the possibility to vary the starting reagents and to chose them among commercially available,

3) the reaction product is precipitated from the cold reaction mixture and can be easily separated by filtration.

The use of Biginelli's reaction in the student workshop allows visually demonstrating to students the strategy of solving a whole range of problems:

- planning the synthesis of compounds with a given structure from several different components;
- obtaining various related heterocyclic compounds based on the same reaction;
- the role of multiple-component reactions in organic synthesis
- modern principles of combinatorial chemistry.

Another important point is the possibility to use this synthesis to demonstrate the achievements of "green chemistry" that characterized with distinctive feature in synthesis of complex molecules in water and other non-toxic liquid media or overall without any solvents. Since the ecological requirements to modern chemistry can not be ignored, the carried out studies are modern and of current importance.

An important factor is also the practical direction of work, in particular, the obtaining biologically active objects, since, as is known, a lot of drugs are created on the basis of heterocyclic compounds. Potentially possible biological activity of the obtained dihydropyrimidones can be studied using a computer program for predicting the biological activity of PASS.

Conclusions. Biginelli's reaction is advisable to be used both in the classical student workshop and in the advanced course of organic chemistry, in particular, the chemistry of heterocyclic compounds. The use of this reaction allows developing new skills in students, attracting them to scientific researches, showing the importance of synthesizing new compounds with potentially useful properties and teaching them how to work with scientific literature and apply theoretical knowledge in practice.

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