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Research Article

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Selectarea Metodei Optimale Pentru Sinteza Dihidropirimidin-2-Onelor(Thione) Folosind Diversi Catalizitori

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Abstract

Recently, the number of publications on the chemistry of 3,4-dihydropyrimidines obtained by condensation under Biginelli reaction conditions has increased significantly. This is due not only to the availability of dihydropyrimidines, but also to their manifestation of a wide range of pharmacological activities: analgesic, anticancer, antifungal, etc. This work provides an incentive for further searches for new compounds of the dihydropyrimidine series and their study.

The relevance of pyrimidines is well known due to their wide range of biological activities due to the different pharmacophoric fragments of their constituent structures. Since they play an important role in human life, and their use in the field of drug research has stimulated the expansion of the range of synthetic production methods, their availability in the laboratory and their chemical transformations, especially in conditions of respect for the protection of ecology and the environment in general. The experiments explored catalysis and its role, their environmental characteristics, pollution, waste and costs, and the application of these concepts to the synthesis of dihydropyrimidines and, as an important member of this series, monastrol. Monastrol, synthesized by a one-step three-component Biginelli reaction in the presence of various bioavailable and biodegradable catalysts, is of significant interest in cancer treatment. Monastrol and related compounds that bind proteins other than tubulin may have less toxicity and fewer side effects than currently used tubulin-binding agents.

Keywords: Dihydropyrimidines, Monastrol, Oxymonastrol, Biginelli Reaction, Ionic Liquids Scopul

Introduction

Recently, the number of publications on the chemistry of 3,4-dihydropyrimidines obtained by condensation under the Biginelli reaction conditions has increased significantly. This is due not only to the availability of dihydropyrimidines, but also to their manifestation of a wide range of pharmacological activities: analgesic, anticancer, antifungal, etc. This activity provides an incentive for further searches for new compounds of the dihydropyrimidine series and their study.

The relevance of pyrimidines is well known due to their wide range of biological activities due to the different pharmacophoric fragments of their constitutive structures. Since they play an important role in human life, and their use in the field of drug discovery has stimulated the expansion of the range of synthetic methods of production, laboratory availability and their chemical transformations, especially under conditions of respect for the protection of ecology and the environment in general. Experiments have explored catalysis and its role, their environmental characteristics, pollution, waste and costs and the application of these concepts to the synthesis of dihydropyrimidines and, as an important member of this series, monastrol. Monastrol, synthesized by a three-component Biginelli reaction in one step in the presence of various bioavailable and biodegradable catalysts, is of significant interest in the treatment of cancer. Monastrol and related compounds that bind proteins other than tubulin may have less toxicity and fewer side effects than currently used tubulin-binding substances.

In the synthesis of dihydropyrimidines, the goal is to select reagents and test different catalysts and conditions, especially in developing strategies to address environmentally friendly catalytic conditions for further use in the work. Eutectic alloys can serve as an alternative to modern toxic and expensive catalysts for such synthesis.

Materials and Methods

To carry out syntheses under the Biginelli reaction conditions, benzaldehydes, ethyl acetoacetate and thiourea or urea were taken in equimolar amounts. The reactions were carried out in the presence of catalysts of eutectic mixtures of ES (0.5 mmol%), at T = 79 0 C for 5.5-7.5 hours, in ethyl alcohol. The results of these works gave good yields of products, with simplicity of the reactions and under rather mild reaction conditions. Identification of the chemical structure of the products was carried out using modern physicochemical methods of analysis. Melting points were determined on a Boetius heating stage. IR spectra were recorded

on a Perkin Elmer Spectrum 100 FT-IR spectrophotometer. 1I, 13C and 15N NMR spectra were recorded on an Avance III Bruker 400 spectrometer (400, 100 and 40.5 MHz) in DMSO-d6. Chemical shifts are reported on the δ scale in ppm. relative to TMS signals. Assignment of signals in the 13C NMR spectra was performed using 1H/13C DEPT, 1H/1H COSY – 45.1H/13C HMQC, 1H/13C HMBC, 1H/1H NOESY, 1H/15N HMQC and 1HMBC/1 experiments. The evolution of the reactions was monitored by TLC on Silufol plates, development with a UV lamp (ʎmax = 254 or 365 nm) and by spraying with an acidic aqueous solution of cerium (III) sulfate or a 20% solution of KMnO4.

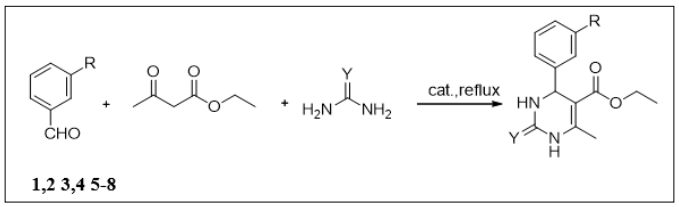


Figure 1: Scheme for the Preparation of Dihydropyridines (5-8).

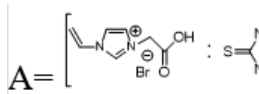
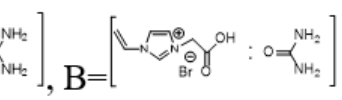
R : H(1), OH(2); Y : O(3), S (4);
5: Y=O, R=H; 6: Y=O, R=OH; 7: Y= S, R=H; 6: Y= S, R=OH

Result

One of the important products of the three-component reaction under Biginelli reaction conditions is monastrol (ethyl-6-methyl-4-(3-hydroxyphenyl)2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxyl). To study the activity of the catalyst, a series of eutectic mixtures based on thiourea and urea were synthesized.

Eutectic mixtures (3-vinyl-imidazolyl acetic acid bromide: thiourea)(A) and (3-vinyl-imidazolyl acetic acid bromide: urea) (B) were obtained, respectively.

Table 1: Preparation of Dihydropyrimidinethiones.

Nu.	Reactiv adehidic	Reactiv Y	Produs	Catalizator: A=  , B= 		R,%	t, ora
				ES	raport		
1	1	3	5	B	1:1	29,0	5 .5
2	1	3	5	B	unsprezece	11.0	5.5
3	2	3	6	B	1:2	54,0	6
4	2	3	6	B	1:2	2 8 .0	6.0
5	1	4	7	A	1:1	1 4 .3	7
6	1	4	7	A	1:1	1 1 .0	7.5
7	2	4	8	A	1:2	1 6 .0	7.5
8	2	4	8	A	1:2	3 3 .0	7.5

Eutectic mixtures were synthesized in ratios of imidazolium salts and thiourea or urea, such as (1:1) and (1:2) and used in the reaction to obtain dihydropyrimidines such as monastrol and oxymonastrol (ethyl-6-methyl-4-(3-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxyl).

Comparative results of the synthesis using eutectic catalysts (3-vinyl-imidazolyl acetic acid bromide:thiourea) and (3-vinyl-imidazolyl acetic acid bromide:urea) in the ratio of 1:1 and 1:2 are presented in Table 1.

Conclusions

Obtaining oxymonastrol (ethyl-6-methyl-4-(3-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxyl) under identical conditions is more efficient than obtaining monastrol: the synthesis proceeds faster in time and the yield of the final product is higher. The advantages of the proposed method are: the availability of the reagents used, the simplicity of the synthesis method and purification of the final product, compliance with the theoretical principles of modern ecology, the characteristics of the maximum approach to environmentally friendly catalytic conditions. The production of oxymonastrol under identical conditions is more efficient than the production of monastrol: the synthesis proceeds faster in time and the yield of the final product is higher.

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