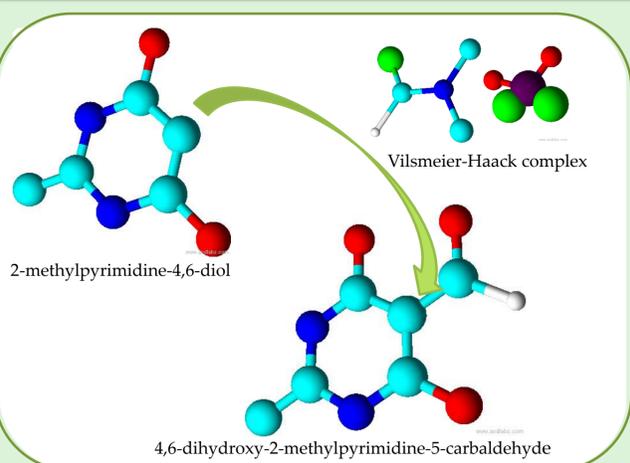


Formylation of 2-methylpyrimidine-4,6-diol under the conditions of the Vilsmeier-Haack reaction

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INTRODUCTION & AIM



Pyrimidine hydroxy derivatives have a rather wide range of biological activities, while possessing a high drug safety profile [1]. Our attention was drawn to 2-methylpyrimidine-4,6-diol (**1**), the 5-formyl derivative of which potentially possesses antihypertensive activity with a high probability (0.8) according to *in silico* screening data [2].

The Vilsmeier-Haack method was chosen to perform the formylation as the most efficient among the known methods for the introduction of a formyl group into heterocyclic systems [3].

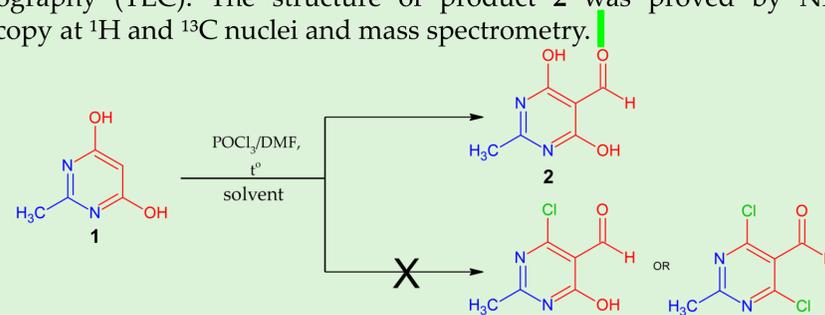
The aim of this work is to study the Vilsmeier-Haack reaction for substrate **1** and to select the optimal solvent for the reaction.

METHOD

In silico bioactivity screening for 4,6-dihydroxy-2-methylpyrimidine-5-carbaldehyde (**2**) was performed using the PASS Online web resource.

The interaction of substrate **1** with Vilsmeier's reagent in a 1:1 ratio gave 4,6-dihydroxy-2-methylpyrimidine-5-carbaldehyde (**2**). The substitution of hydroxyl groups for chlorine observed in reactions with similar substrates did not occur [3] (Sh. 1).

The progress of the synthesis was monitored by thin layer chromatography (TLC). The structure of product **2** was proved by NMR spectroscopy at ¹H and ¹³C nuclei and mass spectrometry.



Scheme 1. Interaction of substrate **1** with Vilsmeier's reagent.

RESULTS & DISCUSSION

Based on the screening data using the web resource PASS Online, product **2** with probability (Probably active) greater than 0.8 is an agonist of I¹-imidazoline receptors, which determines antihypertensive activity.

Regardless of the solvent used, the reaction of substrate **1** with Vilsmeier's reagent in a 1:1 ratio resulted in the formation of product **2**, which is confirmed by NMR spectroscopy data at the ¹H (Fig. 1) and ¹³C nuclei (Fig. 2), as well as by mass spectrometry (Fig. 3).

As a result of this work, the optimal solvent for the above reaction was selected. In DMF medium, product **2** was obtained in the highest practical yield of 61% in 5 hours (tabl. 1).

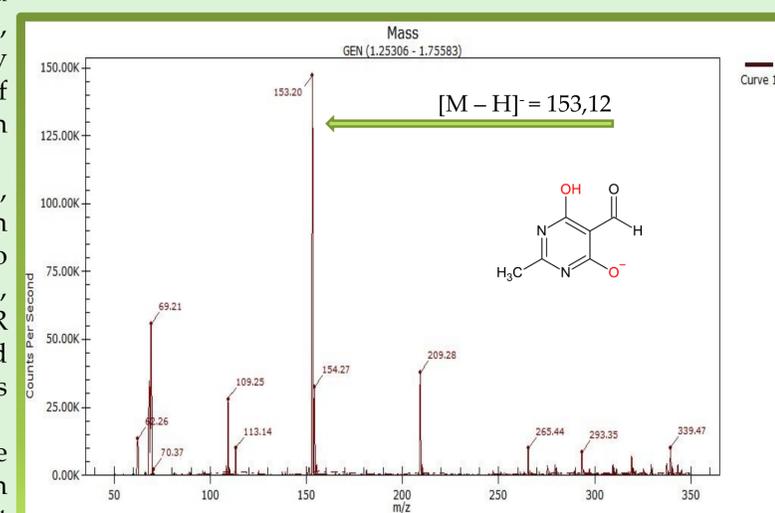


Figure 3. Mass spectrum of product **2** (ESI in negative ion mode).

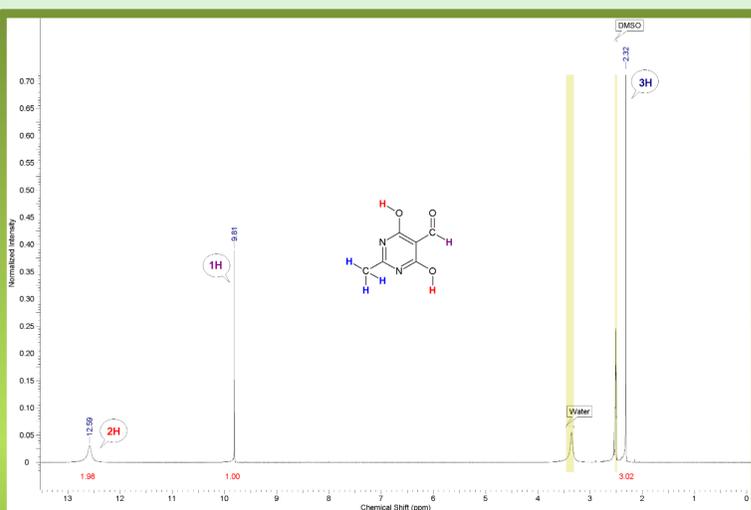


Figure 1. ¹H NMR spectrum of product **2**.

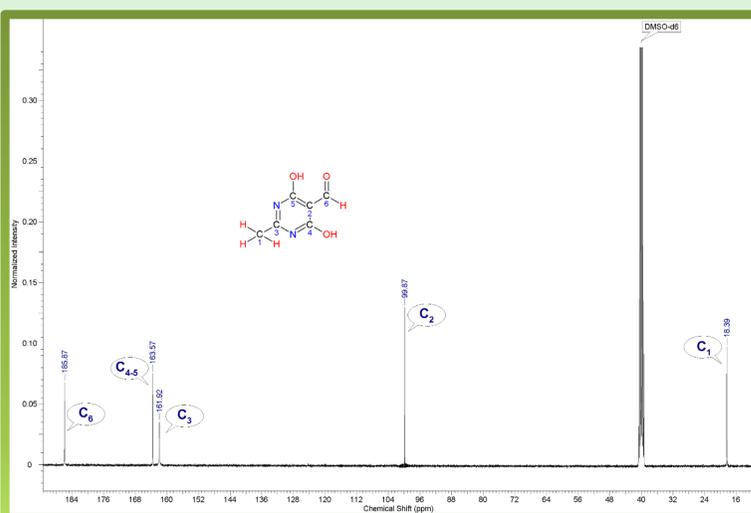


Figure 2. ¹³C NMR spectrum of product **2**.

Solvent	Temperature, °C	Synthesis time, h	Yield, %
DMF	79-81	5	61
1,2-dichloroethane	82-84	6	50
benzene	79-81	6	48
o-xylene	99-101	7	49

Table 1. Dependence of reaction parameters on the solvent used.

CONCLUSION

The reaction of 2-methylpyrimidine-4,6-diol with Vilsmeier's reagent at their equivalent ratio leads to the formation of only 4,6-dihydroxy-2-methylpyrimidine-5-carbaldehyde. Nucleophilic substitution of hydroxyl groups for chlorine does not occur.

The use of DMF as a solvent in the formation of substrate **1** leads to higher practical yield of product **2** and shorter synthesis time compared to benzene, 1,2-dichloroethane and o-xylene.

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