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Formylation of 2-Methylpyrimidine-4,6-diol Under the Conditions of the Vilsmeier-Haack Reaction †

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Abstract: In the course of the work, the influence of the conditions of the Vilsmeier-Haack reaction for 2-methylpyrimidine-4,6-diol (**1**). A comparative analysis of approaches using various solvents (o-xylene, N,N-dimethylformamide (DMF), benzene and dichloroethane) as the reaction medium and the optimal one was selected. During the formylation of substrate 1 in these conditions only 4,6-dihydroxy-2-methylpyrimidine-5-carbaldehyde (**2**). It should be noted that there was no substitution of hydroxyl groups for chlorine atoms observed in reactions with similar substrates. The structure of the resulting product **2** was proved using NMR spectroscopy on ^{1}H and ^{13}C nuclei, and by mass spectrometry.

Keywords: formylation; pyrimidine-4,6-diols; Vilsmeier-Haack reaction; electrophilic substitution

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1. Introduction

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]. To perform the formylation, the Vilsmeier-Haack method was chosen 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.

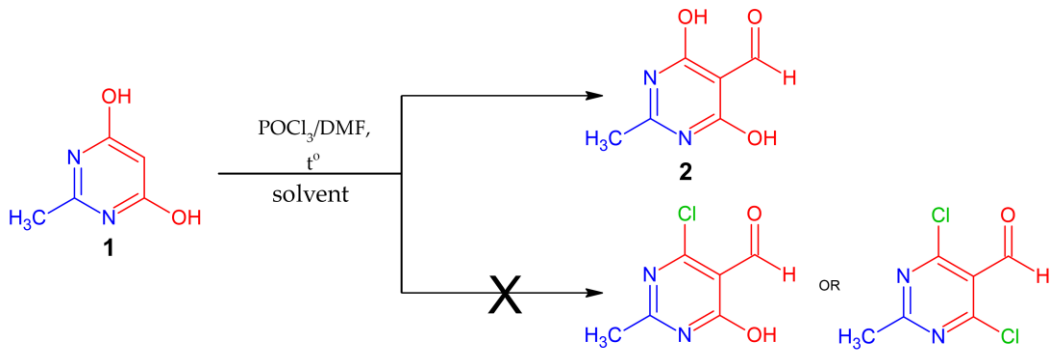
2. Materials and Methods

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] (Scheme 1).

The synthesis was monitored by thin layer chromatography (TLC) in a 1:9 methanol/dichloromethane system with UV detection. The structure of product **2** was proved by NMR spectroscopy at ^{1}H (Figure 1) and ^{13}C (Figure 2) nuclei and by mass spectrometry.

In each individual experiment, strictly equivalent amounts of substrate **1** and Vilsmeier's reagent were taken.



solvent: DMF; 1,2-dichloroethane; benzene; o-xylene.

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

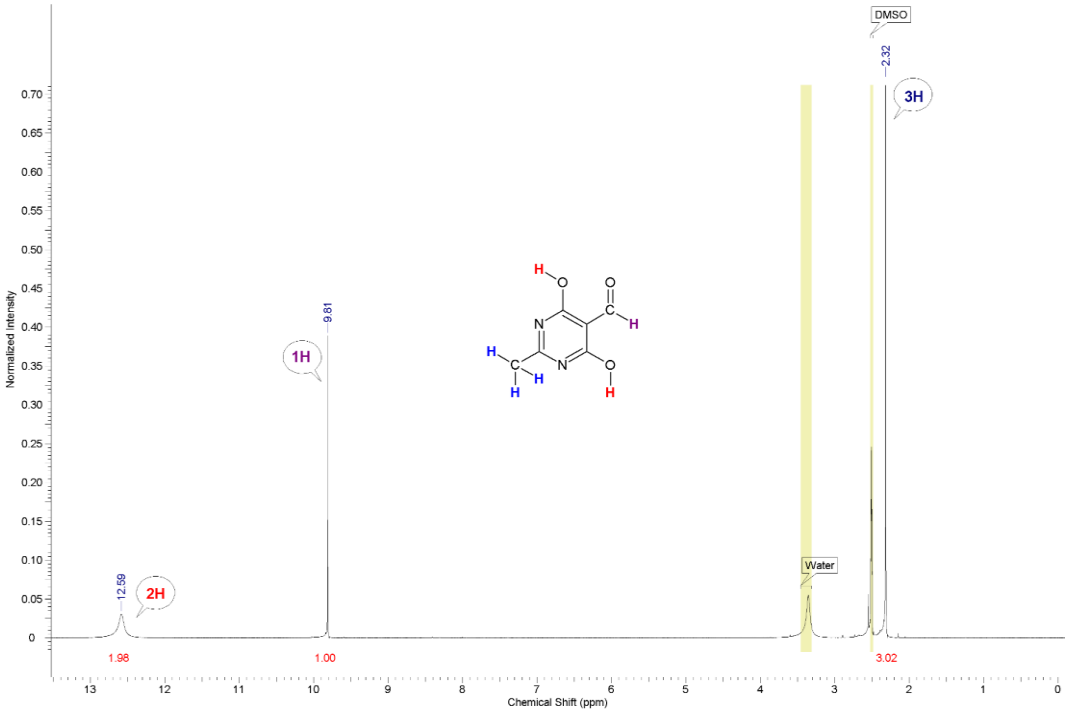


Figure 1. ^{1}H NMR spectrum of product **2**.

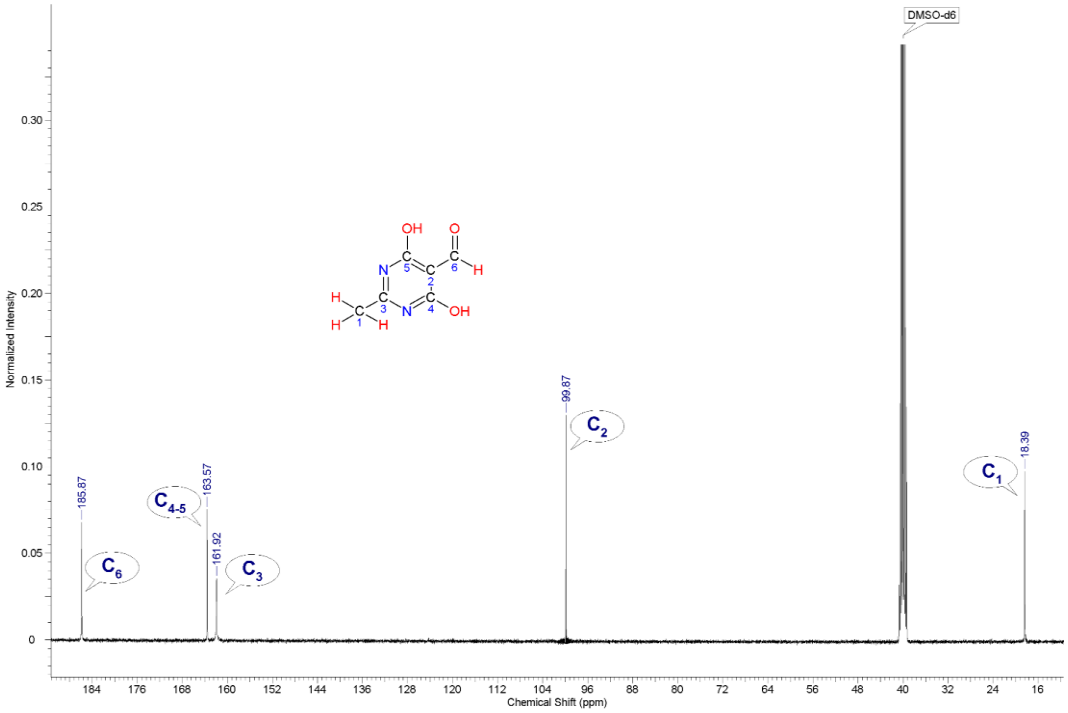


Figure 2. ^{13}C NMR spectrum of product **2**.

2.1. Interaction of 2-Methylpyrimidine-4,6-diol with Vilsmeier's Reagent in Benzene

The prepared and cooled mixture of phosphorus chlorooxide (0.29 mL, 3.16 mmol) and DMF (0.49 mL, 6.3 mmol) under vigorous stirring was added dropwise to a suspension of 0.4 g (3.16 mmol) of substrate **1** in benzene (20 mL). The reaction was boiled with reflux condenser for 6 h. The reaction was monitored by thin layer chromatography in a 1:9 system of methanol and dichloromethane with UV detection for the absence of the starting compound in the reaction mixture. The reaction mixture was poured on ice and stirred overnight. The resulting precipitate was filtered off, then dried at 60 °C. The practical yield of product **2** was 48%.

The NMR spectrum (^1H, DMSO-d6) of the synthesised compound **2** is characterised by the presence of an aldehyde group proton singlet at 9.81 ppm with an integrated intensity of 1. There is also an OH-group proton singlet at 12.59 ppm with an integrated intensity of 1.96 and a methyl group proton singlet at 2.32 ppm with an integrated intensity of 3.02.

The NMR spectrum (^{13}C, DMSO-d6) of the synthesised compound **2** is characterised by signals of methyl group carbon atoms (C_1) in the region of 18.39 ppm, C_2 atom in the region of 99.7 ppm, C_3 in the region of 161.92 ppm, C_4 and C_5 carbon atoms -163.57 ppm and carbon atom of carbonyl group (C_6) in the region of 185.87 ppm.

MS-ESI mass spectrometry: m/z [M-H]- calculated: 153.33; found: 153.20.

2.2. Interaction of 2-Methylpyrimidine-4,6-diol with Vilsmeier's Reagent in 1,2-Dichloroethane

To a suspension of 0.4 g (3.16 mmol) of substrate **1** in 1,2-dichloroethane (20 mL) under vigorous stirring was added carefully dropwise a previously prepared and cooled mixture of phosphorus chlorooxide (0.29 mL, 3.16 mmol) and DMF (0.49 mL, 6.3 mmol). The reaction was boiled with reverse refrigerator for 6 h. The reaction was monitored by thin layer chromatography in a 1:9 methanol/dichloromethane system with UV detection for the absence of the starting compound in the reaction mixture. The reaction mixture was poured on ice and stirred overnight. The resulting precipitate was filtered and dried at 60 °C. The practical yield of product **2** was 50%.

The NMR spectrum (^{1}H, DMSO-d6) of the synthesised compound **2** is characterised by the presence of an aldehyde group proton singlet at 9.79 ppm with an integrated intensity of 1.01, there is also an OH-group proton singlet at 12.53 ppm with an integrated intensity of 2.04 and a methyl group proton singlet at 2.41 ppm with an integrated intensity of 2.96.

The NMR spectrum (^{13}C, DMSO-d6) of the synthesised compound **2** is characterised by signals of methyl group carbon atoms (C_1) in the region of 18.21 ppm, C_2 atom in the region of 99.56 ppm, C_3 in the region of 161.13 ppm, C_4 and C_5 carbon atoms -163.69 ppm and carbon atom of carbonyl group (C_6) in the region of 185.55 ppm.

MS-ESI mass spectrometry: m/z [M-H]- calculated: 153.33; found: 153.11.

2.3. Interaction of 2-Methylpyrimidine-4,6-diol with Vilsmeier's Reagent in DMF

The prepared and cooled mixture of phosphorus chloroxide (0.29 mL, 3.16 mmol) and DMF (0.49 mL, 6.3 mmol) under vigorous stirring was carefully added dropwise to a suspension of 0.4 g (3.16 mmol) of substrate **1** in DMF (3 mL). The reaction was incubated at 80 °C for 5 h. The reaction was monitored by thin layer chromatography in a 1:9 methanol/dichloromethane system with UV detection for the absence of the starting compound in the reaction mixture. The reaction mixture was poured on ice and stirred overnight. The resulting precipitate was filtered off and dried at 60 °C. The practical yield of product **2** was 61%.

The NMR spectrum (^{1}H, DMSO-d6) of the synthesised compound **2** is characterised by the presence of an aldehyde group proton singlet in the region of 9.8 ppm with an integrated intensity of 0.96, there is also an OH-group proton singlet in the region of 12.6 ppm with an integrated intensity of 2.20 and a methyl group proton singlet in the region of 2.31 ppm with an integrated intensity of 2.94.

The NMR spectrum (^{13}C, DMSO-d6) of the synthesised compound **2** is characterised by signals of methyl group carbon atoms (C_1) in the region of 18.91 ppm, C_2 atom in the region of 99.34 ppm, C_3 in the region of 161.35 ppm, C_4 and C_5 carbon atoms -163.54 ppm and carbon atom of carbonyl group (C_6) in the region of 185.76 ppm.

MS-ESI mass spectrometry: m/z [M-H]- calculated: 153.33; found: 153.47.

2.4. Interaction of 2-Methylpyrimidine-4,6-diol with Vilsmeier's Reagent in o-Xylene

The prepared and cooled mixture of phosphorus chloroxide (0.29 mL, 3.16 mmol) and DMFA (0.49 mL, 6.3 mmol) was added dropwise to a suspension of 0.4 g (3.16 mmol) of substrate **1** in o-xylene (20 mL) under vigorous stirring. The reaction was incubated at 100 °C for 7. The reaction was monitored by thin layer chromatography in a 1:9 methanol/dichloromethane system with UV detection for the absence of the starting compound in the reaction mixture. The reaction mixture was poured on ice and stirred overnight. The resulting precipitate was filtered off and dried at 60 °C. The practical yield of product **2** was 49%.

The NMR spectrum (^{1}H, DMSO-d6) of the synthesised compound **2** is characterised by the presence of an aldehyde group proton singlet in the region of 9.91 ppm with an integrated intensity of 0.94, there is also an OH-group proton singlet in the region of 12.58 ppm with an integrated intensity of 1.89 and a methyl group proton singlet in the region of 2.54 ppm with an integrated intensity of 3.13.

The NMR spectrum (^{13}C, DMSO-d6) of the synthesised compound **2** is characterised by signals of methyl group carbon atoms (C_1) in the region of 18.23 ppm, C_2 atom in the region of 99.44 ppm, C_3 in the region of 161.33 ppm, C_4 and C_5 carbon atoms -163.78 ppm and carbon atom of carbonyl group (C_6) in the region of 185.45 ppm.

MS-ESI mass spectrometry: m/z [M-H]- calculated: 153.33; found: 153.01.

3. Results and Discussion

Based on the PASS Online screening data, product **2** has a probability (Probably active) greater than 0.8 of being an agonist of I^1-imidazoline receptors, which accounts for its antihypertensive activity.

I1-imidazoline receptors, which is responsible for the 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 ^1H (Figure 1) and ^{13}C nuclei (Figure 2), as well as by mass spectrometry (Figure 3).

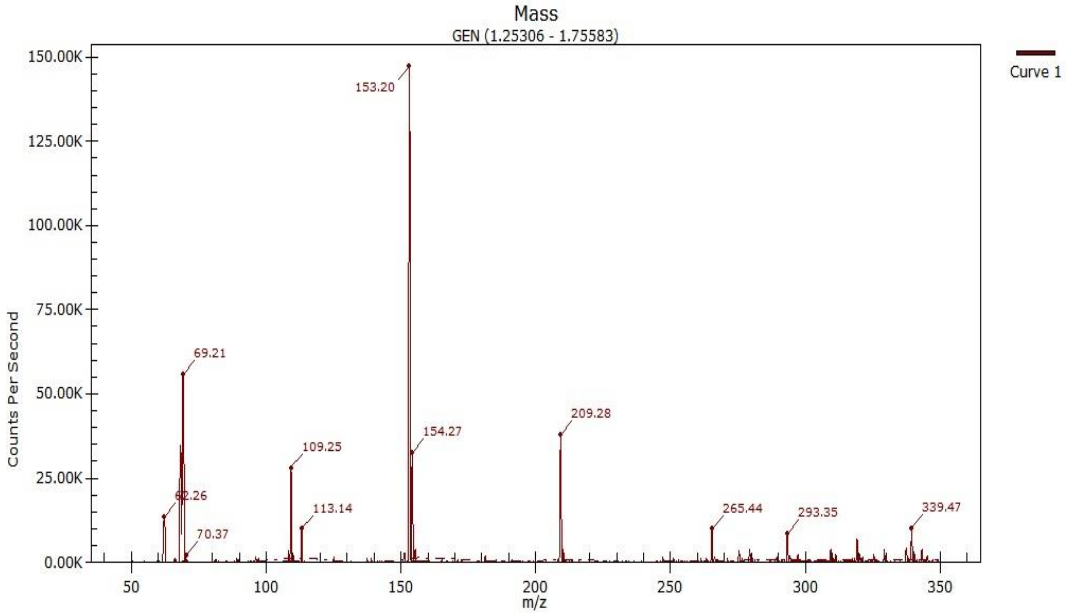


Figure 3. Mass spectrum of product **2** (ESI in negative ion mode).

As a result of this work, the optimal solvent for the above reaction was selected. In DMF medium, product **2** was obtained with the highest practical yield of 61% at a holding time of 5 h (Table 1).

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

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

4. Conclusions

Reaction of 2-methylpyrimidine-4,6-diol with Vilsmeyer's reagent at their equivalent ratio leads to the formation of only 4,6-dihydroxy-2-methylpyrimidine-5-carbaldehyde. Substitution of hydroxyl groups observed on similar substrates to the chlorine atom did not occur.

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

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