IRSTI 31.21.27 https://doi.org/10.26577/ijbch.2020.v13.i1.15

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Synthesis of substituted tetrahydropyran-4-one and its oxime

Abstract, Tetrahydropyranone derivatives are promising starting materials for the synthesis of various heterocyclic compounds with biological activity. Oximes obtained on the basis of heterocyclic compounds, which include 3,5-substituted tetrahydropyran-4-one, possess antibacterial activity. We studied the optimal conditions for the synthesis of 3,5 substituted tetrahydropyran-4-one and its oxime, to confirm the obtained structures, and to perform quantum-chemical calculations of the conformations of the target compounds. The optimal method for the 3,5-dimethyleneoxytetrahydropyran-4-one (III) synthesis was the condensation of acetone with formaldehyde in a ratio of 1:4 in the presence of K_2CO_3; the yield was 67.4 %. The reaction of (III) with hydroxylamine hydrochloride was studied in the presence of NaOH and AcONa at different temperatures. The optimal yield (65.3%) of the product (IV) was obtained in the presence of AcONa with heating below 80 ^{0}C. To determine the composition of obtained compounds elemental analysis was used. Functional composition and structural elements were identified using IR spectroscopy. To prove the structure of the synthesized oxime, ^{1}H and ^{13}C NMR spectra were taken on a JNN-ECA Jeol 400 spectrometer (at a frequency of 399.78 MHz and 100.53 MHz) with a $CDCl_3$ solvent. Quantum-chemical calculations of stable conformations of (III) and (IV) was performed using *ab initio* DFT B3LYP method and 6-31G (d) and 6-311+G(3df,2p) basis sets. Calculated total energies and dipole moments allow to find the geometry of the most stable conformers. The most stable conformer of (IV) is the 3a5a configuration of substituents, which can be explained by the formation of intramolecular hydrogen bonds. Calculations show that the syn- and anti-isomers of 3,5-dimethyleneoxytetrahydropyran-4-one oxime are energetically equivalent.
Key words: tetrahydropyranone, acetone, formaldehyde, oxime, synthesis, condensation, conformational analysis.

Introduction

Pyran systems are an important group of six-membered oxygen-containing heterocycles that have diverse biological properties; they are found in many natural compounds [1-2]. Tetrahydropyranones can serve as precursors in the fine organic synthesis of new biologically active compounds. In medicine and modern technologies, substituted tetrahydropyran-4-ones, their derivatives [3-5] and isomers [6-7] are widely used.

Oximes of aldehydes and ketones are used to protect and selectively activate groups, to produce amides and nitriles. They act as intermediates in many reactions, such as the production of amides by Beckmann rearrangement [8]. Oximes find application in transition-metal catalysis [9-12]. Oximes and their ethers are present in some biologically active compounds that exhibit healing properties [13-14]. Tetrahydropyran-4-one linker-containing oximes show the antiproliferative activity [15].

3,5-dimethyleneoxytetrahydropyran-4-one and its oxime were synthesized in order to obtain their derivatives to study their properties and biological activity.

Earlier, we reported on synthesis and quantum chemical calculations of the conformation of 3,5-substituted tetrahydropyranone [16]. Theoretical calculations of the conformation of the obtained oxime were also performed. In order to confirm structures, NMR ^{13}C and ^{1}H spectra were studied.

Materials and methods

Earlier, we reported on the synthesis of oxime of 3,5-dimethyleneoxytetrahydropyran-4-one (IV) [16]. In the present work we studied the different conditions of 3,5-substituted tetrahydropyranone synthesis according to the scheme below.

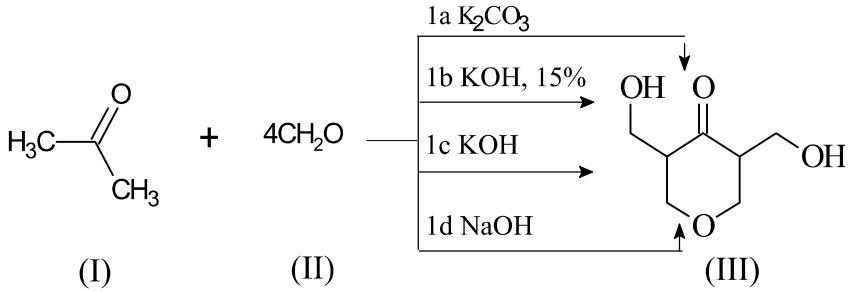

Figure 1 – Synthesis of 3,5-substituted tetrahydropyranone

1a) The method of (III) synthesis in the presence of K_2CO_3 is described in the article [16]. Yield is 67.4 %.

1b) 11.6 g (0.2 mol) of acetone, a formalin solution containing 0.8 mol of formaldehyde, 15% KOH solution (0.04 mol) were added to a round bottom flask equipped with a mechanical stirrer. It was refluxed for 7 days at a temperature of 35-40 ^{0}C. To control the reaction by TLC, the mobile phase ethanol-hexane (6: 4) was used. To develop chromatographic zones, the plate was treated with iodine vapor. Yield was 65.7 %.

1c) A formalin solution containing 0.8 mol of formaldehyde, 2.24 g of KOH (0.04 mol) were added in a flask. After stirring and cooling of the reaction mixture, 11.6 g (0.2 mol) of acetone were added. The reaction takes place within a few minutes with the release of heat. Yield is 58.2 %.

1d) Similar to procedure 1c, but instead of KOH, 1.6 g of NaOH (0.04 mol) were added. Yield was 56.8 %.

In order to study the conditions of (IV) synthesis we carried out the reaction of equivalent amounts of (III) and hydroxylamine hydrochloride in an alkaline medium and in the presence of sodium acetate according to the scheme [17].

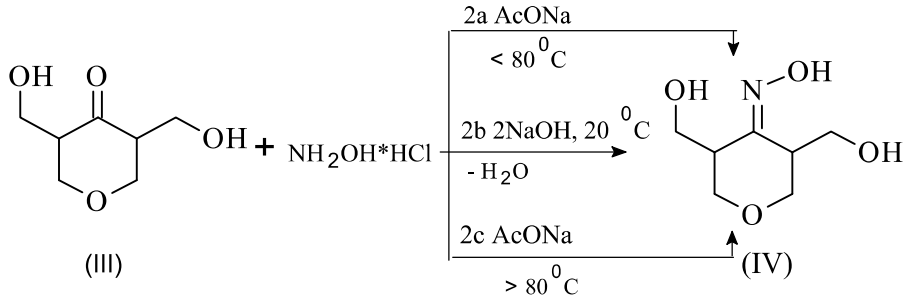

Figure 2 – Synthesis of 3,5-dimethyleneoxytetrahydropyran-4-one oxime

2a) 1.5 g (0.02 mol) of hydroxylamine hydrochloride (15% water solution), 3.2 g (0.02 mol) of (III) (ethanol solution) and 2 g of AcONa (0.02 mol) were added to a round-bottom flask. The reaction mixture was refluxed and heated (< 80 °C) for 40 minutes. After completion of the reaction, 60 g of cold water were added and the unreacted (III) was filtered off. Pieces of ice were added to the filtrate and acidified with sulfuric acid. The resulting product was filtered and dried at 70-80 °C. Yield was 65.3 % in the powder form.

2b) 1.6 g (0.01 mol) of (III) and 0.75 g (0.01 mol) of hydroxylamine hydrochloride in sodium hydroxide were added to a round bottom flask. The reaction mixture was stirred and refluxed at 20 °C for 7 days. The progress of the reactions was monitored by TLC

in the system butanol: acetic acid: water (40:12.5:29). After completion of the reaction, 50 ml of benzene and desiccant (calcium chloride) were added. Calcium chloride was filtered off and the mixture was washed again with benzene. The product was separated by vacuum distillation in the form of a brown powdery substance. Yield was 62.5 %.

2c) Similar to method 2.1, but at temperature above 80 °C. Yield was 60.9 %.

Results and discussion

The condensation of acetone and formaldehyde in a ratio of 1: 4 was studied under mild alkaline conditions in the presence of K_2CO_3 (1a). The product (III) yield was 67.4 %, while the reaction time was 7 days. Heating above 50 °C leads to the formation of by-products and a decrease in the yield of the reaction. In the presence of a 15% KOH solution (1b), the product yield was 65.7 %. In the presence of KOH (1c) or NaOH (1d) side reactions of polymerization occur, which reduces the yield of the product (58.2 % and 56.8 % respectively). Thus, method 1a is optimal (Table 1).

Reactions of (III) with hydroxylamine hydrochloride in the presence of CH_3COONa and NaOH were investigated at different temperatures. In the presence of sodium acetate, (IV) was synthesized with 65.3% yield at the most optimum state and high flow rate, at a temperature below 80 °C (Table 2).

The physical constants of recrystallized purified (III) and (IV) were determined. The results are shown in Table 3.

The low melting range of the obtained compounds indicates the purity of the isolated substances. The functional groups were identified by the results of IR spectra. The results of the IR spectrum analysis are shown in Table 4.

Table 1 – Optimization of (III) synthesis by condensation of acetone[1] and formaldehyde[2]

Entry	Molar ratio	Solvent	Temperature, ^{0}C	Time	Yield, %
1a	1^1: 4^2: 0.1 (K_2CO_3)	water	35-40	7 days	67.4
1b	1^1: 4^2: 0.2 (KOH)	water	35-40	7 days	65.7
1c	1^1: 4^2: 0.2 (KOH)	water	25	3-5 min.	58.2
1d	1^1: 4^2: 0.2 (NaOH)	water	25	3-5 min.	56.8

Table 2 – Optimization of (IV) synthesis by reaction of (III)[1] with hydroxylamine hydrochloride[2]

Entry	Molar ratio	Solvent	Temperature, ^{0}C	Time	Yield, %
2a	1^1: 1^2: 1 (AcONa)	water	< 80	40 min	65.3
2b	1^1: 1^2: 1 (NaOH)	water	20	7 days	62.5
2c	1^1: 1^2: 1 (AcONa)	water	80-90	40 min	60.9

Table 3 – Physical constants of (III) and (IV)

Product	T_m, °C	R_f (ethanol-hexane (6: 4)	Yield, %
1a	138-140	0.210	67.4
1b		0.228	65.7
1c		0.230	58.2
1d		0.215	56.8
		R_f (butanol: acetic acid: water (40:12.5:29)	
2a	128-129	0.410	65.3
2b		0.413	62.5
2c		0.411	60.9

Table 4 – The results of the IR spectrum of (III) and (IV)

Compound	Frequency, ν, cm^{-1}				
	C=O	OH	C-O-C	CH_2	C-C
III	1703	3432	1101	2933,29	1657,14
	C=N	N-OH	C-O-C	CH_2	C-C
IV	1650	3414	1180.93	2892	1657

To identify the structure of the synthesized compounds, ^1H and ^{13}C NMR spectra were obtained. The ^1H NMR spectra were recorded on a JNN-ECA Jeol 400 spectrometer (at a frequency of 399.78 MHz) with a solvent $CDCl_3$ (Table 5).

The ^{13}C NMR spectra were recorded on a JNN-ECA Jeol 400 spectrometer (at a frequency of 100.53 MHz) with a solvent $CDCl_3$. The results are given in Table 6.

As reported in a previous article, we carried out the conformational analysis of (III) using the methods of quantum chemistry. The ab-initio calculation method and results were described there [16]. Similar calculations were performed for (IV). The results are shown in Table 7.

According to the calculations, one of the stable geometry of 3,5-dimethyleneoxytetrahydropyran-4-one is the conformation (III)3a5a in which the substituents are located in the axial position.

Table 5 – ^1H NMR spectra of (III) and (IV)

Compound	Chemical shift, σ				
	$CH_2(C^{2,6})$	CH ($C^{3,5}$)	$CH_2(C^{7,8})$	OH(^{9,10})	OH(^{11})
III	3.61 (dd)	2.19 (tp)	3.53 (tp)	5.15 (tp)	-
IV	3.82 (dd)	1.61 (tp)	3.03 (tp)	5.25 (tp)	6.8 (s)

Table 6 – ^{13}C NMR spectrum of (III) and (IV)

Compound	Chemical shift, σ			
	$CH_2(C^{2,6})$	CH (C)	$CH_2(C^{7,8})$	C^4
III	66.18	50.39	62.02	215.19
IV	51.37	30.95	44.76	157.19

Table 7 – Total energy and dipole moment of (IV) conformations calculated by the DFT method B3LYP density functional and the 6-31G basis sets

Conformation	Total energy, Hartree	Dipole moment, Debye
(IV) 3e5e	-626.16560	4.76
(IV) 3a5e	-626.16183	0.94
(IV) 3e5a	-626.16715	1.07
(IV) 3a5a	-626.17215	4.46

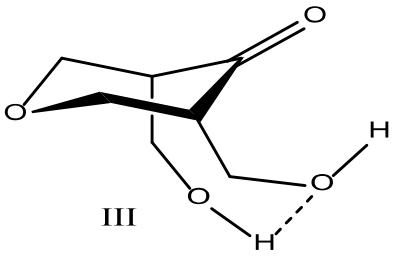

Figure 3 – The conformation (III)3a5a

This may be explained by the formation of intramolecular hydrogen bonds between the hydroxyl groups. The difference from the molecule of (III), where the energy (III) 3e5e is quite low and approaches the value of the (III) 3a5a conformation energy, for oxime (IV) conformation 3a5a is the most stable (Table 7). This can be explained by the interaction with the functional group of (IV).

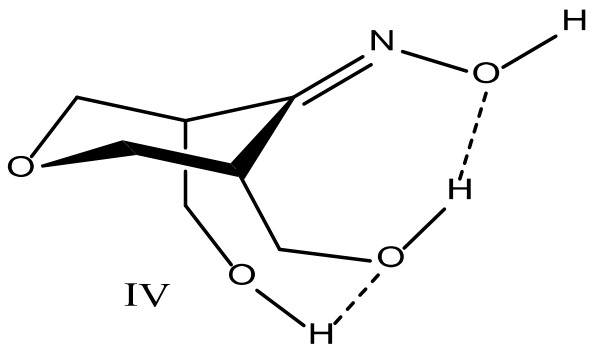

Figure 4 – The conformation (IV)3a5a

For oximes, syn- and anti-isomerism are characteristic. However, due to the symmetric arrangement of the substituents, no significant differences in energy were revealed for the syn- and anti-isomers of oxime.

Conclusion

Based on the processing of experimental data, optimal synthesis conditions of 3,5-dimethyleneoxytetrahydropyran-4-one synthesis by acetone and formaldehyde condensation are determined. It has been established that the basicity of the reaction mixture has the greatest influence on the yield of the product. An increase in temperature affects the side processes of polymerization. The presence of concentrated alkalis also leads to an increase in temperature (due to an exothermic reaction) and side reactions, which reduces the yield of the product. Therefore, methods 1c and 1d give a lower product yield compared to methods 1a and 1b. The optimal condition for the condensation of acetone and formaldehyde is the presence of potassium carbonate and heating no higher than 40 ^{0}C (1a). In the presence of K_2CO_3 at 40 ^{0}C the product yield was 67.4%. The methods 1a and 1b are highly time-dependent, but more economical in reagent requirements.

For the production of oxime, the optimal conditions were the presence of AcONa and heating not higher than 80 ^{0}C (2a method). Yield of product was 65.3%. Method 2b gives a higher yield than 2c, but depends more on the reaction time. An increase in temperature above 80 ^{0}C reduces the yield of the product.

The structure of the synthesized compounds was determined and identified by IR spectroscopy, elemental analysis and NMR spectroscopy. The obtained experimental data can be used to develop a technological scheme for the production of 3,5 substituted tetrahydropyran-4-one and its oxime.

Quantum-chemical calculations of stable conformations of 3,5-dimethyleneoxytetrahydropyran-4-one oxime was performed. The total energies and dipole moments of the conformers are calculated. The most stable is the 3a5a configuration of substituents, which can be explained by the formation of intramolecular hydrogen bonds. The syn- and anti-isomers of 3,5-dimethyleneoxytetrahydropyran-4-one oxime are energetically equivalent. A more detailed conformational analysis of 3,5 substituted tetrahydropyran-4-one and its oxime can be carried out after obtaining two-dimensional ^{13}C and ^{1}H NMR spectra.

Acknowledgments

NMR spectroscopy analysis was performed on the equipment of the research laboratory «NMR spectroscopy», the Sh. Ualikhanov Kokshetau State University.

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