ALKYLATION REACTIONS OF QUINAZOLIN-4-ONE

Saitkulov Foziljon Ergashevich[1]
Elmuradov Burkhon Zhuraevich[2]
O'lmasova Komilakhon Mo'minjon qizi[3]
Alijonova Asalxon Odiljon qizi[4]
[1]Tashkent State Agrarian University,
[2]Institute of Chemistry of Plant Substances
Academy of Sciences of the Republic of Uzbekistan
[3-4]Student of Tashkent State Agrarian University
E-mail:fsaitkulov@bk.ru
https://doi.org/10.5281/zenodo.7536590

Annatation: For the first time methylation of quinazolin-4-one by "soft" and "hard" alkylation agents (methyl iodide, dimethylsulfate, methyltosylate) in proton polar ethanol, aproton apolar, aproton dipolar solvents (dioxane-1,4, acetonitrile, dimethyl formamide, dimethyl sulfoxide) was studied. It was shown, that the reaction goes in two directions on atom nitrogen N-3 and oxygen O-4. It is find, that N-3/O-4 relation depends on nature of methylation agents, solvent and temperature.

Key words: methylation, qinazolin-4-on, "soft" and "hard", alkylation agents, methyl iodide, dimethylsulfate, methyltosylate, proton polar ethanol, aproton apolar, aproton dipolar solvents, dioxane-1,4, acetonitrile, dimethyl formamide, dimethyl sulfoxide, atom nitrogen N-3 and oxygen O-4, nature of methylation agents, solvent, temperature.

INTRODUCTION

It is known that methylation of pyrimidine and quinazoline derivatives proceeds in different directions with the formation of one or two isomers [1-9]. So, if 2-oxoquinazolin-4-one is methylated along the N-1 and N-3 atom or simultaneously along these two centers [2], then the methylation of 2-thioxoquinazolin-4-one proceeds mainly along the "soft" reaction center the sulfur atom [3]. The second possible isomer of 2-thioxo-3-methylquinazolin-4-one is formed in small quantities [1,3]. Methylation of 2-aminoquinazolin-4-one by methylating agents of various natures proceeds mainly along the N-3 atom [5]. In the case of using "hard" agents, for example, methyltosylate, depending on the nature of the solvent, methylation products are also formed by the atom O-2 2-oxoquinazoline-4-one, O-4 2-oxo-, -thioxo-, -methylthio-, -amino-, -methylaminoquinazolin-4-ones [2,5]. Therefore, in the case of these substrates, a change in the direction of the alkylation reaction can be expected.

THE EXPERIMENTAL PART

^{1}H NMR spectra were recorded on a UNITY 400 plus spectrometer (Varian) with an operating frequency of 400 MHz in a mixture of CCl_4+DMSO-d_6 solvents. Gexamethyldisiloxane (GMDS) was used as an internal standard in the ^{1}H NMR spectra.

Prearation of 4-chloroquinazolin-4-one

(2 mmol) of quinazolin-4-one and (12 mol) of phosphorus chloroxide were placed in the ampoule. The ampoule was sealed and heated in an oil bath at 140ºC for six hours. After that, the reaction mass was cooled, dissolved in benzene, washed with a 5% solution of sodium hydroxide base and the solvent was distilled after the usual treatment. 0,421gr (81%) of the product was isolated with a melting point = 206º C (heptane). R_f=0,88 (benzene: acetone 5:2).

Preparation of 4-methoxyquinazolin-4-one

A mixture of 0,146 g (1 mol) of 4-chloroquinazolin-4-one and 15 ml of sodium methylate solution obtained by dissolving 0,023 g of 1 (mmol) sodium in methanol was boiled for two hours. Cooled, diluted with water, dried. 0,2 g (72%) of the product was isolated with a melting point = 262ºC(ethanol).

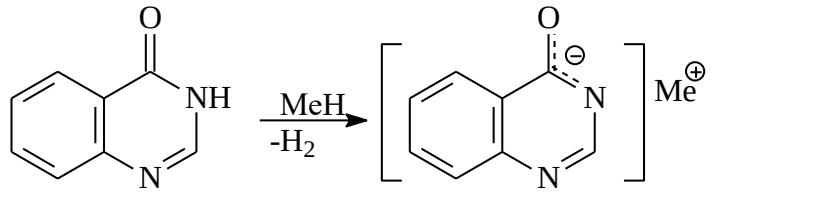
R_f=0,89 (benzene: acetone 5:2).

General method of methylation of quinazolin-4-one

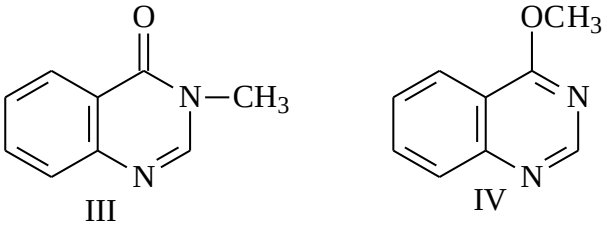
To a solution or suspension (0,005 mmol) of quinazolin-4-one in 50 ml of absolute solvent, sodium hydride (0,005 mmol) was added and mixed for 30 minutes. Drops (0,005 mmol) of methyl iodide (dimethyl sulfate, methyltosylate) were added to 1 ml of solvent. The reaction mixture was stirred at 20-25ºC for 24 hours or at 80-90ºC for 4 hours, the solvent was driven off, the remainder was treated with water. The precipitate was filtered, washed with water and dried. The isomer composition and isomer ratio were determined by ^{1}H NMR spectroscopy.

In this work, we decided to use the simplest representative of their quinazolin-4-one as an methylation agent. In the molecule of this compound, the methylation reaction should mainly involve nitrogen atom N-3 and oxygen O-4. The possibility of N-1 nitrogen atom participating in the reaction is unlikely due to the presence of an N-1-C2 double bond.

The quinazolin-4-one molecule [I] under the action of alkali metal hydrides forms anions, [II] in which the negative charge is redistributed along the N-3-C-4-O-4 system:



The ambident anion of the sodium salt is alkylated by the action of acetylating agents along the N-3 and O-4 atom. Indeed, methylation of the sodium salt with methyl iodide, dimethyl sulfate or methyltosylate proceeds along these atoms to form 3-methylquinazoline-4-one [III] and 4-methoxyquinazoline [IV].



Methylation of the sodium salt of quinazolin-4-one was carried out with methyl iodide, dimethyl sulfate and methyltosylate. Nonpolar dioxane-1,4, polar proton ethanol, polar aprotic acetonitrile, polar aprotic solvents dimethylformamide (DMFA) and dimethyl sulfoxide (DMSO) were used as a solvent. The reactions were carried out at 20-25°C and when heated in a water bath (80-90°C). The results obtained are shown in the table.

Ratios of N^3/O^4 isomers during methylation of quinazolin-4-one. Table 1

1	quinazolin-4-one	dimethyl sulfate	Alcohol	80-90	-
2	quinazolin-4-one	methyl iodide	Alcohol	80-90	N^3-96, O^4-9
3	quinazolin-4-one	methyl iodide	Alcohol	20	N^3-100
4	quinazolin-4-one	dimethyl sulfate	Alcohol	20	-
5	quinazolin-4-one	methyltosylate	Alcohol	80-90	N^3-100
6	quinazolin-4-one	methyltosylate	Alcohol	20	-
7	quinazolin-4-one	methyl iodide	DMFA	80-90	O^4-100
8	quinazolin-4-one	methyl iodide	DMFA	20	N^3-100
9	quinazolin-4-one	dimethyl sulfate	DMFA	20	N^3-100
10	quinazolin-4-one	dimethyl sulfate	DMFA	80-90	N^3-100
11	quinazolin-4-one	methyltosylate	DMFA	80-90	-
12	quinazolin-4-one	methyltosylate	DMFA	20	-

13	quinazolin-4-one	methyl iodide	Acetonitrile	20	-
14	quinazolin-4-one	methyl iodide	Acetonitrile	80-90	-
15	quinazolin-4-one	methyltosylate	Acetonitrile	80-90	-
16	quinazolin-4-one	methyltosylate	Acetonitrile	20	-
17	quinazolin-4-one	dimethyl sulfate	DMSO	80-90	N^1-5, N^3-87,O^4-8
18	quinazolin-4-one	dimethyl sulfate	DMSO	20	N^3-100
19	quinazolin-4-one	methyltosylate	DMSO	80-90	-
20	quinazolin-4-one	methyltosylate	DMSO	20	-
21	quinazolin-4-one	dimethyl sulfate	Dioxane-1.4	80-90	N^3-60, O^4-40
22	quinazolin-4-one	methyl iodide	Dioxane-1.4	80-90	N^3-100
23	quinazolin-4-one	methyl iodide	Dioxane-1.4	20	N^3-40, O^4-60
24	quinazolin-4-one	dimethyl sulfate	Dioxane-1.4	20	-

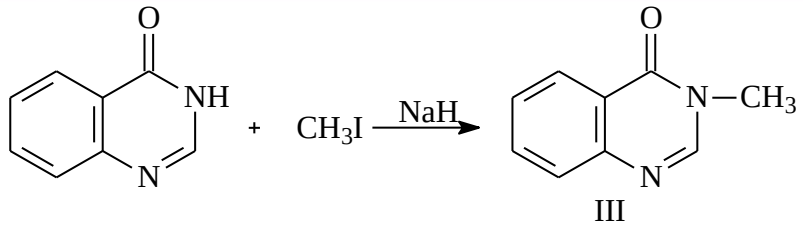
As can be seen from the data given in the table, methylation of the sodium salt with methyl iodide in ethanol, dioxane-1,4, acetonitrile leads to the formation mainly of the N-3-methylation product of quinazoline-4-one (III), which is explained by the "softens" of the N-3 nitrogen atom and the methylating agent, which is correlated by the Pearson's principle [8]. The proportion of 4-methoxyquinazoline (IV) increases during the reaction under heating (80-90ºC).

When switching to "hard" methylating agents - dimethyl sulfate and methyltosylate, the ratio of N-3/O-4 decreases significantly.

It was almost 1:3 for methyl iodide and dimethyl sulfate in ethanol, as well as in acetonitrile. When using DMFA and DMSO, the fraction (III) decreases sharply or does not form at all.

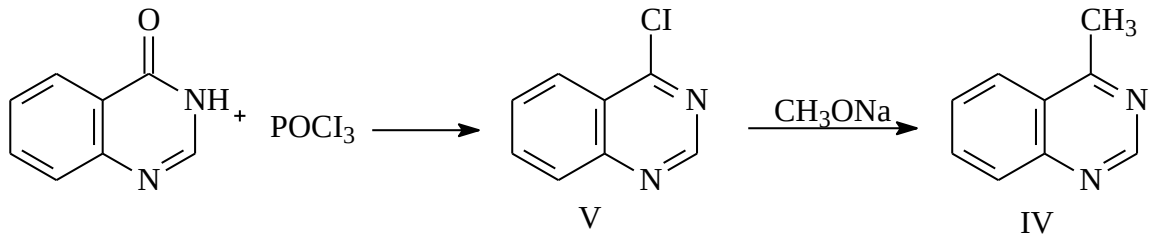
The ratio of N-3/O-4 isomers was determined by measuring the relative integral intensity of methyl group protons in N-3 and O-4. The chemical shifts of these protons were compared with those for 3-methylquinazoline-4-one ((III)) and 4-methoxyquinazoline (IV).

Compound 3 was synthesized by methylation of 1 with methyl iodide in ethanol in the presence of sodium hydride according to the scheme:



III

The synthesis of compound (IV) was carried out from (I) and phosphorus chloride with subsequent treatment of the resulting 4-chloroquinazoline (V) with sodium methylate in absolute methanol according to the reactiones:



V IV

Thus, it was revealed that the methylation of quinazolin-4-one, in contrast to the corresponding quinazoline-4-ones, proceeds mainly through two reaction centers N-3 and O-4.

Literature:

1.Fozil E.Saitkulov, Azamat A.Tashniyazov, Azimjon A.Mamadrahimov, Kh.M Shakhidoyatov. 2,3-Di¬methyl¬quinazolin-4(3H)-one. 2014/7/1. magazine Acta Crystallographica Section E: Structure Reports Online. №7 pp.o788-o788.

2.Саиткулов Ф. Э., Гиясов К., Элмурадов Б. Ж. Метилирование 2-метилхиназолин-4-она «мягкими» и «жесткими» метилирующими агентами //Universum: химия и биология. – 2022. – №. 11-2 (101). – С. 49-51.

3. Саиткулов Ф.Э., Элмурадов Б.Ж., Гиясов К. АЛКИЛИРОВАНИЯ ХИНАЗОЛИН-4-ОНА "МЯГКИМ" И "ЖЕСТКИМ" АЛКИЛИРУЮЩИМИ АГЕНТАМИ // Universum: химия и биология : электрон. научн. журн. 2022. 1(103) стр. 53-57.

4. Saitkulov, F. E. Ropijonova, N.SH,Elmuradov, B. J. (2022). Methylation of Quinazolin-4-One with "Soft" and "Hard" Methylating Agents. International Journal of Development and Public Policy, 1(8), 97–101.

5. G.O. Boymuratova, F.E. Saitkulov, Kh.M. Nasimov, J. G'.Rahimov, & M.Tugalov. (2022). To Examine the Processes of Biochemical Action Of 6-Benzylaminopurine with Cobalt-II Nitrate Dihydrate on the "Morus Alba" Variety of Moraceae Plant. Eurasian Journal of Physics,Chemistry and Mathematics, 3, 39–42.

6. Саиткулов Ф. Э., Элмурадов Б. Ж. УФ-спектральные характеристики хиназолин-4-он и –тионов. Innovative developments and research in education international scientific-online conference. pp-10-12

7. Saitkulov f. et al. biochemical nutrition family plant rute-lemon leaved //Академические исследования в современной науке. –2022. –Т. 1. – №. 17. –С. 268-273.
8. Murodillayevich, Kholmirzaev Mekhroj, Khaydarov Gayrat Shoyimovich, and Saitkulov Foziljon Ergashevich. "Chromoto-Mass Methods for Detecting Simple Esters in Chromatography-Mass Spectrometry Method." INTERNATIONAL JOURNAL OF BIOLOGICAL ENGINEERING AND AGRICULTURE 1.6 (2022): 53-56.
9. Saitkulov, Foziljon, et al. "CARBOHYDRATES ARE THE MAIN SOURCE OF ENERGY IN THE BODY." Solution of social problems in management and economy 1.7 (2022): 68-71.
10. Ergashevich, Saitkulov Foziljon, et al. "Photochemical Processes Photosynthesis Pathway On House Plants Leaves" Black Prince"." Texas Journal of Agriculture and Biological Sciences 10 (2022): 76-78.
11. Saitkulov, Foziljon, et al. "THE ROLE IN THE PLANT AND THE FUNCTIONS OF NUTRIENTS." Инновационные исследования в науке 1.16 (2022): 29-31.
12. Saitkulov, F., Eshqobilov, J., Turgunova, N., & Xamidov, A. (2022). PLANT NUTRITION, THE PROCESS OF ABSORPTION. Current approaches and new research in modern sciences, 1(7), 25-29.
13. Saitkulov, Foziljon, et al. "TITRIMETRIC ANALYSIS OF CALCIUM CATION IN" OBI NAVVOT" VARIETY OF MELON." Академические исследования в современной науке 1.19 (2022): 302-304.
14. Saitkulov, Foziljon, et al. "BIOCHEMICAL EFFECTS OF THE COORDINATION COMPOUND OF COBALT-II NITRATE QUINAZOLIN-4-ONE WITH 3-INDOLYL ACETIC ACID IN THE “AMBER” PLANTS GRADES PHASEOLUS AUREUS." Академические исследования в современной науке 1.17 (2022): 263-267.
15. Saitkulov, F., Khudayarov, M., Hikmatova, D., Sharipova, K., & Khamidov, A. (2022). QUANTITATIVE METHOD FOR THE DETERMINATION OF NITRATE USING DIPHENYLAMINE. Theoretical aspects in the formation of pedagogical sciences, 1(6), 187-190.
16. Saitkulov, Foziljon, et al. "STUDY OF THE EFFECT OF FERTILIZING ON GRAIN PRODUCTIVITY." Development and innovations in science 1.17 (2022): 32-35.
17. Saitkulov F. et al. PLANT NUTRITION, THE PROCESS OF ABSORPTION //Current approaches and new research in modern sciences. – 2022. – Т. 1. – №. 7. – С. 25-29.
18. Saitkulov F. et al. RECOMMENDATIONS FOR THE USE OF FATS //Theoretical aspects in the formation of pedagogical sciences. – 2022. – Т. 1. – №. 7. – С. 175-177.

19. Saitkulov F. et al. THE ROLE IN THE PLANT AND THE FUNCTIONS OF NUTRIENTS //Инновационные исследования в науке. – 2022. – Т. 1. – №. 16. – С. 29-31.

20. Saitkulov, F., Qilichyeva, N., Abdullayev, B., Anvarov, A., & Ergasheva, M. (2022). TITRIMETRIC ANALYSIS OF CALCIUM CATION IN" MEGATON" VARIETY OF CABBAGE. International Bulletin of Applied Science and Technology, 2(10), 134-135.