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Methylation of Quinazolin-4-One with "Soft" and "Hard" Methylating Agents

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Annotation: For the first time methylation of qinazolin-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.

Keywords: 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).

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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

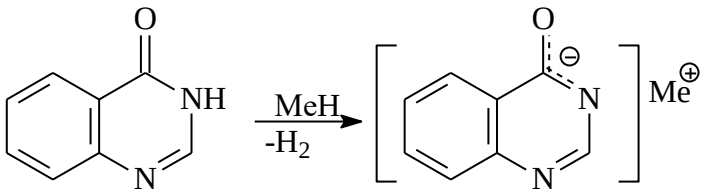
To a solution or suspension (0,005 mmol) of quinazolin-4-one in 50 ml of absolute solvent, sodium hydride (0,005 mmol) was added and mixed for 30 minutes. Drops (0,005 mmol) of methyl iodide (dimethyl sulfate, methyltosylate) were added to 1 ml of solvent. The reaction mixture was stirred at 20-25ºC 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.

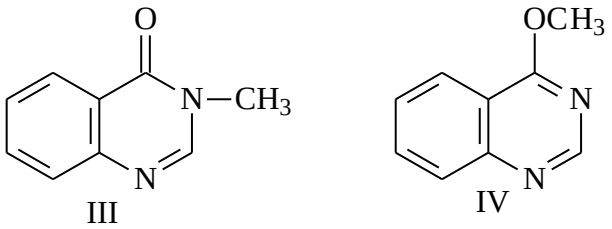
The quinazolin-4-one molecule [I] under the action of alkali metal hydrides forms anions, [II] in which the negative charge is redistributed along the

N-3-C-4-O-4 system:



I II Me = Li,Na,K

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].



III 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

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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

№	Solvent	Methylating agent	Temperature	Ratioisomers in %		
	1	2	3	N^1	N^3	O^4
1	Ethanol	methyl iodide	20-25	-	100	-
2	Ethanol	methyl iodide	80-90	-	96	4
3	Ethanol	dimethyl sulfate	20-25	-	100	-
4	Ethanol	dimethyl sulfate	80-90	-	-	-
5	Ethanol	methyltosylate	20-25	-	-	-
6	Ethanol	methyltosylate	80-90	-	100	-
7	Dioxane-1,4	methyl iodide	20-25	-	40	60
8	Dioxane-1,4	methyl iodide	80-90	-	-	100
9	Dioxane-1,4	dimethyl sulfate	20-25	-	-	-
10	Dioxane-1,4	dimethyl sulfate	80-90	-	40	60
11	Dioxane-1,4	methyltosylate	20-25	-	80	20
12	Dioxane-1,4	methyltosylate	80-90	-	74	26
13	Ацетонитрил	methyl iodide	20-25	-	-	-
14	Ацетонитрил	methyl iodide	80-90	-	40	60
15	Ацетонитрил	dimethyl sulfate	20-25	-	-	-
16	Ацетонитрил	dimethyl sulfate	80-90	-	100	-
17	Ацетонитрил	methyltosylate	20-25	-	-	-
18	Ацетонитрил	methyltosylate	80-90	-	100	-
19	Dimethylformamide	methyl iodide	20-25	-	100	-
20	Dimethylformamide	methyl iodide	80-90	-	100	-
21	Dimethylformamide	dimethyl sulfate	20-25	-	100	-
22	Dimethylformamide	dimethyl sulfate	80-90	-	100	-
23	Dimethylformamide	methyltosylate	20-25	-	100	-
24	Dimethylformamide	methyltosylate	80-90	-	100	-
25	Dimethyl sulfoxide	methyl iodide	20-25	-	100	-
26	Dimethyl sulfoxide	methyl iodide	80-90	5	87	8
27	Dimethyl sulfoxide	dimethyl sulfate	20-25	-	100	-
28	Dimethyl sulfoxide	dimethyl sulfate	80-90	-	100	-
29	Dimethyl sulfoxide	methyltosylate	20-25	-	100	-
30	Dimethyl sulfoxide	methyltosylate	80-90	-	100	-

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.

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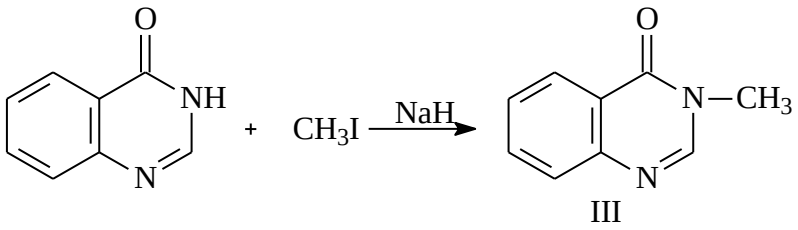
It was almost 1:3 for methyl iodide and dimethyl sulfate in ethanol, as well as in acetonitrile. When using DMFA and DMSO, the fraction (III) decreases sharply or does not form at all.

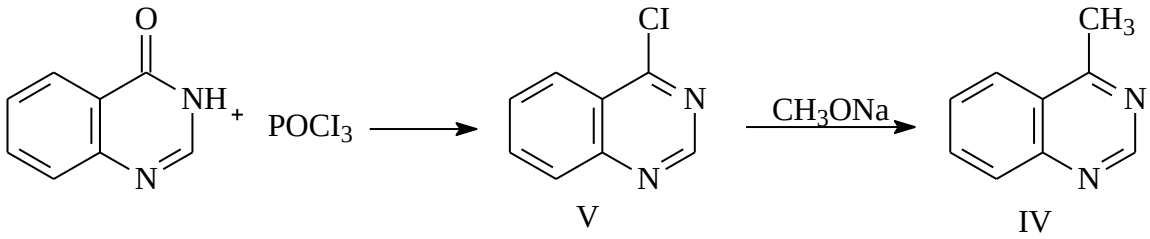
The ratio of N-3/O-4 isomers was determined by measuring the relative integral intensity of methyl group protons in N-3 and O-4. The chemical shifts of these protons were compared with those for 3-methylquinazoline-4-one ((III)) and 4-methoxyquinazoline (IV).

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.

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