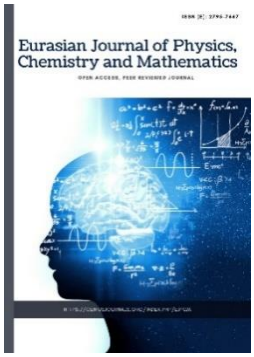

Influence of the nature of the methyling agent and solvent on the directions of the methylation reaction of 2-methylqinazolin-4-ones

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ABSTRACT

It is known that methylation of pyrimidine and quinazoline derivatives proceeds in different directions with the formation of one or two isomers. So, if 2-methilquinazolin-4-one is methylated at the N-1 and N-3 atom or simultaneously at these two centers, then methylation of 2-methyilquinazolin-4-one occurs mainly at the "softer" reaction center

Keywords: *quinazoline, methylation of pyrimidine, 2-oxoquinazolin-4-one is methylated at the N-1 and N-3 atom, 2-methilquinazolin-4-one*

Introduction

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

In the toric ratio, the N-1 center can also participate in the reaction, although the formation of methylation products at it is unlikely, simpler 2H, -methyl-, -phenyl-, -p-nitrophenylquinazolin-4-ones (1-4) in various solvents is undoubted theoretical interest. ^{1}H NMR spectra were recorded on a UNITY 400 plus spectrometer (Varian) with an operating frequency of 400 MHz in a CCl_4 + DMSO-d_6 solvent mixture. Hexamethyldisiloxane (HMDS)

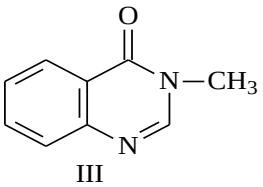
was used as an internal standard in the ^{1}H NMR spectra[1-16].

Method and results

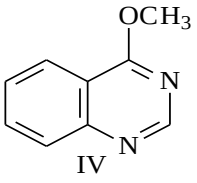
Sodium hydride (0,005 mmol) was added to a solution or suspension (0,005 mmol) of 2H, -methyl-, -phenyl-, -p-nitrophenylquinazolin-4-ones in 50 ml of an absolute solvent, and the mixture was stirred for 30 minutes. Added dropwise (0,005 mmol) methyl iodide (dimethyl sulfate, methyl tosylate) in 1 ml of solvent. The reaction mixture was stirred at 20-25ºC for 24 hours or at 90-95ºC for 4 hours, the solvent was distilled off, the residue was treated with water. The precipitate formed was filtered off, washed with water, and dried. The isomeric composition and ratio of isomers were determined by ^{1}H NMR spectroscopy.

In this work, we decided to use their simplest representative, quinazolin-4-one, as the methilating agent. In the molecule of this compound, the methylation reaction should mainly involve the nitrogen atom N-3 and oxygen O-4. The possibility of participation in the reaction of the nitrogen atom N-1 is unlikely due to the presence of the N-1-C-2 double bond.

The ambident anion of the sodium salt is alkylated by the action of methylating agents at the N-3 and O-4 atom. Indeed, methylation of the sodium salt with methyl iodide, dimethyl sulfate, or methyl tosylate occurs at these atoms to form 3-methylquinazolin-4-one [III] and (or) 4-methoxyquinazoline [IV].



III



IV

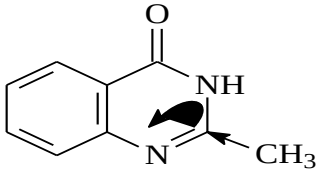
Methylation of the sodium salt of quinazolin-4-one was carried out with methyl iodide, dimethyl sulfate, and methyl tosylate. The solvent used was nonpolar dioxane-1,4, polar protic ethanol, polar aprotic acetonitrile, polar aprotic solvents dimethylformamide (DMF) and dimethyl sulfoxide (DMSO).

The excremental part

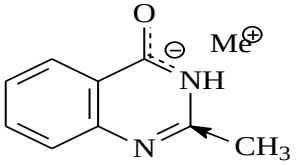
1.48 g (0.01 mol) 2-methylquinazolin-4-one, 0.56 g (0.01 mol) KOH, and 50 mL DMFA were added to a round-necked flask equipped with a reflux condenser with a chlorcalcium tube, a thermometer, a separatory funnel, and a mechanical stirrer. 1.06 ml (r=1.33g/cm3) (0.01mol) of methyl iodide solution in 5ml DMFA was added dropwise through a separatory funnel, mixed with a solution of the obtained 2-methylquinazolin-4-one potassium salt. The mixture was stirred at room temperature (20°C) for 24 h. Then 100 ml of water was added, extracted with chloroform, dried over dry Na_2SO_4. After removing the solvent, the remaining residue was recrystallized from hexane to give 1.4 g of 2,3-dimethylquinazolin-4-one in 80% yield and 0.25 g of 1,2-dimethylquinazolin-4-one in 20% yield.

Conclusion

The introduction of an electron-donating methyl group into the second position of the quinazolin-4-one molecule leads to an increase in the total density of atoms in the pyrimidine ring.

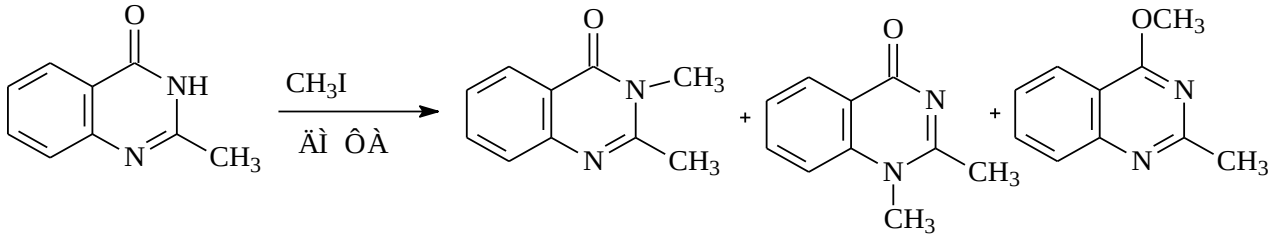


First of all, the basic nature of N^3 and N^1 atoms increases. This effect also applies to the oxygen atom in C^4=O. Electron delocalization of the ambident anion formed under the action of alkali of 2-methylquinazolin-4-one also changes.



$Me^{\oplus}$= Na, K, Li

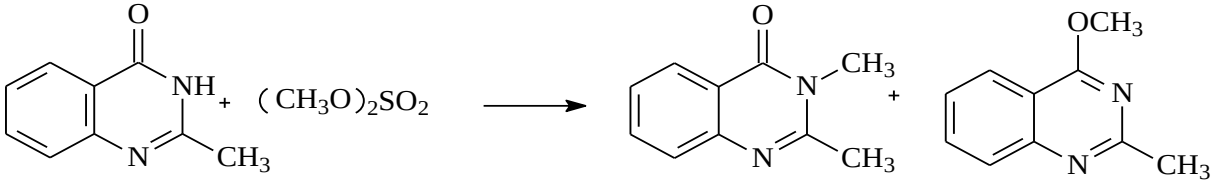
Alkylation of 2-Methylquinazolin-4-one with methyl iodide and dimethylsulfate in alcohol proceeds only with the formation of 2,3-dimethylquinazolin-4-one, that is, the reaction proceeds selectively to the N-3-atom. When aproton dipolar DMFA is used as a solvent and the alkylating agent CH_3I 1,3-dimethylquinazolin-4-one is formed along with this compound.



The ratio of isomers formed in this depends on the temperature. For example, the reaction is 80% and 20% at 20°C, and 73% and 37% at 80-90°C.

In contrast, when 2-methylquinazolin-4-one is methylated with dimethylsulfate in DMFA at 20°C, it goes to the nitrogen atom in the third position.

A mixture of 2,3-dimethylquinazolin-4-one and 2-methyl-4-methoxyquinazoline is formed when the reaction is carried out at room temperature at 80-90°C.



It is worth mentioning that the proportion of N-3 and O-4 isomers is equal.

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