European Scholar Journal (ESJ)
Available Online at: https://www.scholarzest.com
Vol. 3 No.11, November 2022
ISSN: 2660-5562

ALKYLATION OF 2H (ALKYL)-SUBSTITUTED PYRIMIDINONES-4

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Article history:
Received: 1st September 2022
Accepted: 1st October 2022
Published: 4th November 2022

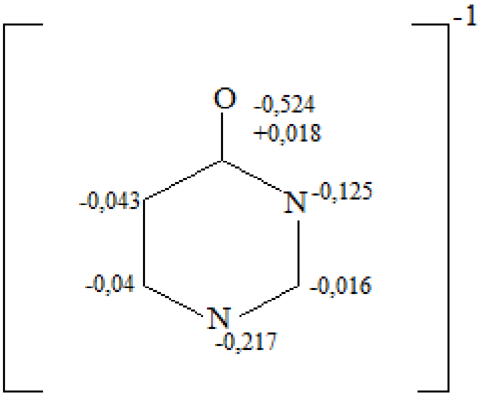
Abstract:
We have studied the alkylation reactions of pyrimidinons-4 with nigher alkyl halides. It was shown that, depending on the methyl iodide and methyl tosylate, the alkylation of pyrimidinones-4 with higher alkyl halides in absolute alcohol proceeds with the formation of a mixture of isomeric N-3 and O-4 alkyl products.

Keywords: Alkyl, Substituted, Pyrimidine, Pyrimidinone, Product, Methyl Tosylate, Methyl Iodide, Alkylhalide.

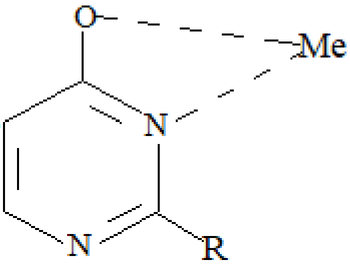
The first representative of pyrimidines, containing a hydroxyl group in position 4, pyrimidinone-4 and its 2-alkyl (methyl-, ethyl-, trifluoromethyl-) substituted belong to simple ambident systems of this series. In these compounds, the negative charge is localized on the oxygen atom [1]. However, in this case, there is another significant factor that plays an important role in alkylation reactions, this is the polarizability of the nitrogen atom in the 3rd position.

Based on the spectral data, it was assumed that the negative charge, along with the oxygen atom, is also localized on the N-3 atom [2-4]

The electron distribution below for pyrimidines-4 shows that the nitrogen atom is more polarizable than oxygen. Calculations show that approximately 75% of the negative charge in the pyrimidinone-4 anion is distributed between N-3 and the oxygen atom

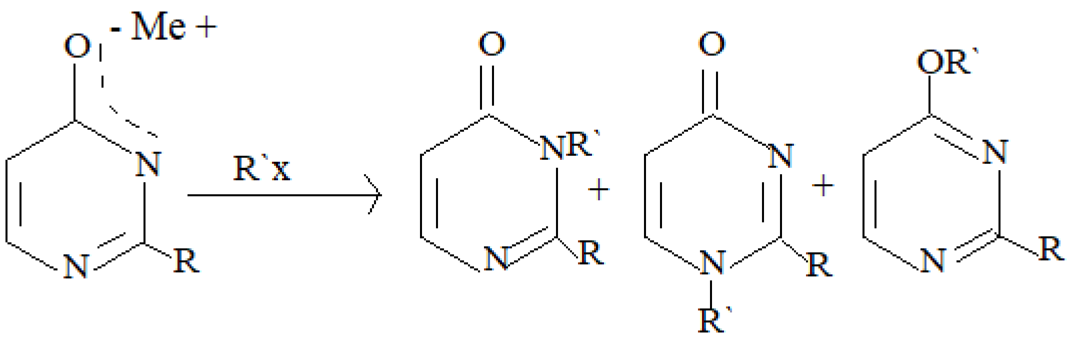


For these compounds, the authors allowed the existence of an anion with the participation of a hydroxyl group, i.e., the coordination of the metal with oxygen, although here one should assume



R=H, CH_3, C_2H_5, CF_3

The formation of an ambident anion with the involvement of the O=C=N system. When these anions are alkylated, the reaction can proceed in three directions: at the oxygen atom, N3 and N1.



The alkylation reaction of pyrimidinone-4, 2-methyl-, -ethyl, trifluoromethylpyrimidinone-4 with methyl, ethyl, isopropyl iodides is of the second order and the rate constants were: 3.34 (R=H, R`=CH3), 1.84 (R =R'=CH3), 1.41 (R=C2H5, R'=CH3), 2.28 (R=H, R'=C2H5), 1.70 (R=H, R'=iso-C3H7) l.mol-1sec-1 x × 103.

From these data, it can be seen that the rate of alkylation decreases with increasing volume of the alkyl group of the alkylating agent, as well as the substituent in position 2.

The reaction of 2-trifluoromethylpyrimidinone-4 with methyl iodide proceeds in the other direction, affecting the N3 and O centers. The O/N3 ratio of the products was 3:2. Alkylation of the oxygen atom 2H, -methylethylpyrimidinones-4 occurs already during the transition to ethyl bromide; this forms a mixture consisting of three products. The isomeric composition (O/N3/N1) is 2.4:6.6:1 (R=H), 1.4:2.4:1 (R=CH3), 3.8:2.9:1 (R=C2H5) respectively.

Thus, with an increase in the volume of the substituent of the alkyl group of the alkylating agent, the direction of the reaction changes towards the formation of the O-alkylation product. So, when interacting with isopropyl bromide, even in the case of unsubstituted pyrimidinone-4, 55% of 4-isopropyloxypyrimidine is formed. 32% 3- and 13% 1-isopropylpyrimidinone-4 were also obtained. The reaction of 2-methyl-4-ethylpyrimidinone-4 with isopropyl bromide occurs exclusively at the oxygen atom. Similar results were obtained in the bottling of the sodium salt of pyrimidinone-2 [5]; these authors came to this conclusion on the basis that pressure does not affect the distribution of products during the alkylation of ambident anions.

The nature of the solvent dramatically changes the direction of the pyrimidinone-4 alkylation reaction. Solvents that promote the formation of free ions (DMF, diglyme, methanol) equally affect the distribution of isomers during the alkylation of sodium, potassium, and lithium salts of the studied pyrimidinones-4. This becomes clear when one considers that the effect of the cation is minimal because it is ionized by the solvent.

Influence of the nature of the solvent on the ratio of isomers in the alkylation of the sodium salt of 2-methylpyrimidinone-4 with ethyl bromide.

(0.45m, 40˚C)

table number 1

№	Растворитель	Время реакции, час	Изомерный состав		
			O	N^3	N^1
1	ДМФА	17	29	50	21
2	Метанол	13	25	59	16
3	Изо-пропанол	5	17	47	36
4	этилацетат	24	5	5	90

As can be seen from the data given in Table No. 1, the use of ethyl acetate sharply changes the direction of the reaction, that is, it proceeds preferentially along the N-1 atom. This fact is explained by the fact that the sodium salt of pyrimidinone-4 is poorly soluble in this solvent, so the role of the cation is essential in this case.

Alkylation of the silver salt of pyrimidinone-4 in benzene gives products at the oxygen atom and N-3 in a ratio of 5:1.

Methylation of 2-methylpyrimidinone-4 sodium salt with methyl iodide

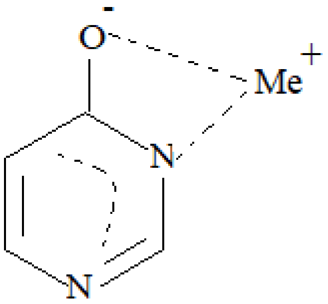
(0.45m, 40˚C)

table number 2

№	Растворитель	Время реакции, час	Изомерный состав	
			N^3	N^1
1	$HCONH_2$	7	53	47
2	H_2O	2	45	55
3	ДМСО	7	80	20
4	CH_3OH	5	66	34
5	CH_3OCH_3	11	38	62
6	$H\text{-}C_3H_7OH$	8	46	54

7	Изо-C_3H_7OH	8	53	47
8	$CH_3COOC_2H_5$	8	12	88
9	ТГФ	240	-	100

Methylation in THF gives only 1-methylpyrimidinone-4, that is, the nitrogen atom in position 1 undergoes alkylation. Thus, a solvent with low solvating power, along with the coordination of the cation with the oxygen atom, blocks the nitrogen atom N-3 as shown in the structure below:



The homogeneity of the reaction medium is important in alkylation reactions. Thus, its role was shown by the example of phenoxide ions [6].

Alkylation in such solvents as isopropyl alcohol, n-butanol, acetone showed that the reaction starts heterogeneously. Then, as in the case of DMF, it is homogenized. In the case of ethyl acetate, the reaction proceeds completely under heterogeneous conditions.

Conclusion:

Thus, in this article, we have shown that with an increase in the dielectric constant of the solvent, the salt becomes more soluble and the reaction proceeds faster, and vice versa, its decrease leads to a decrease in the reaction rate.

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