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INVESTIGATION OF THE NUCLEOPHILIC REARRANGEMENT OF 2-(CYANOMETHYL)-1,4,6-TRIMETHYLPYRIMIDINIUM IODIDE INTO 4,6-DIMETHYL-2-METHYLAMINO-NICOTINIC ACID NITRILE

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2-(Cyanomethyl)-1,4,6-trimethylpyrimidinium iodide is rearranged into 4,6-dimethyl-2-methylamino-nicotinic acid nitrile by interaction with alcoholic solutions of sodium ethylate, methylamine, and also glycine and β-alanine ethyl esters. This conversion was also observed for the first time for pyrimidinium salts during the process of recording ^{1}H NMR spectra in CD_3OD solution containing CD_3ONa. After the rearrangement deuterium exchange of the protons of the pyridine ring methyl groups was noted spectrally. It was demonstrated experimentally that for carrying out and completing the recyclization a quantity of nucleophilic reagent must convert the molar equivalent quantity of pyridinium salt.

Keywords: 2-alkylaminonicotinonitrile, pyrimidinium salt, deuterium exchange, Kost–Sagitullin nucleophilic rearrangement.

The present communication, devoted to the study of the influence of a nitrile group located in the side chain of a pyrimidinium salt, on the Kost–Sagitullin rearrangement, continues the series of studies on the recyclization of pyrimidinium salts into 2-alkylaminopyridine derivatives [1-4]. The model for investigation, 2-(cyanomethyl)-1,4,6-trimethylpyridinium iodide (**3**), was synthesized by the reaction of 2-(carbamoylmethyl)-4,6-dimethylpyrimidine (**1**) with P_2O_5 and subsequent methylation of the obtained nitrile **2** with methyl iodide.

As was shown by our experiments, the introduction of an electron-withdrawing group (nitrile) into the side chain of a pyrimidinium salt enables the rearrangement to take place. In alcoholic sodium ethylate solution salt **3** is rearranged in a few minutes into 4,6-dimethyl-2-methylaminonicotinonitrile (**4**) in close to quantitative yield. On heating in alcoholic methylamine solution the same recyclization occurs in 72% yield. It is appropriate to note that under analogous conditions the iodoalkylates of esters and amides of the corresponding substituted 2-pyrimidinylacetic acids are rearranged in an overall yield of 30-55% [3-5].

It is also interesting that isomerization of salt **3** into pyridine **4** was observed by us even under the action of such amines as glycine and β-alanine ethyl esters. However under these conditions "rearrangement and transamination" [1], i.e. with the inclusion of an amino acid fragment into the reaction product, was not recorded.

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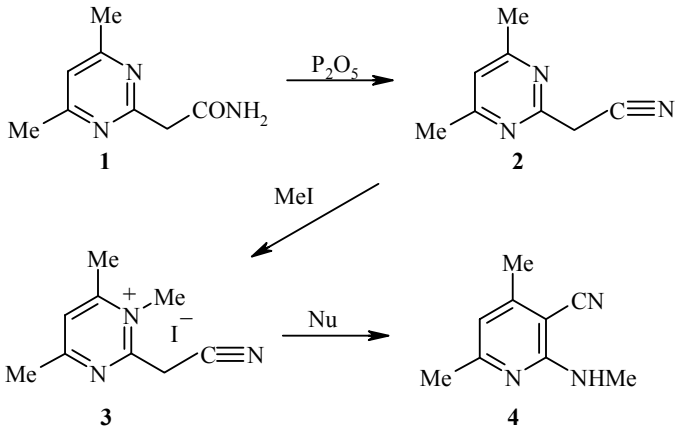


Nu = EtONa, $MeNH_2$, H_2NCH_2COOEt, $H_2NCH_2CH_2COOEt$

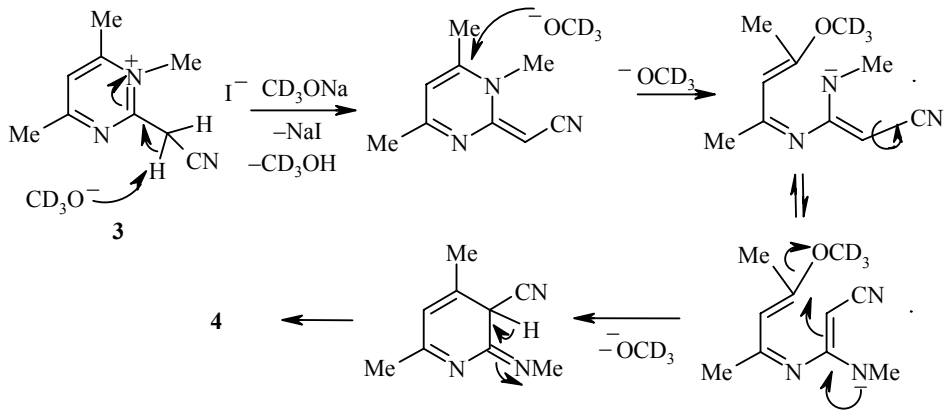
The ease with which the rearrangement of iodide **3** occurs in alcoholic sodium ethylate solution (rapid process and high yield of reaction product) stimulated us to study the process of converting salt **3** into pyridine **4** in CD_3OD solution containing CD_3ONa within the dynamics of NMR spectral changes.

It turned out that after adding a small quantity of CD_3ONa to a solution of iodide **3** in CD_3OD the recyclization product was already formed after 5-10 min. This was indicated by the appearance in the ^1H NMR spectrum of signals belonging to the protons of the reaction product. In particular there were singlets at 2.17 and 2.26 (4- and 6-CH_3), 5.94 (5-H), and 3.15 ppm (N-CH_3). However it is necessary to note that the signals of the protons of the initial salt were retained in the spectrum even on the following day, and the ratio of the intensities of the signals of both substances were practically unchanged over the course of time.

On adding a large quantity of CD_3ONa to the ampul disappearance of the proton signals of salt **3** from the ^1H NMR spectrum was noted already after 5 min, while the signals of the recyclization product protons were retained. The shape of the spectrum indicated completion of the rearrangement and was confirmed chromatographically.

We consider that the incomplete conversion described above of the initial salt in the experiment with CD_3ONa (insufficiency of the latter) possibly indicates the formation at the first reaction step of an anhydro form as a result of fission of proton from the methylene group. Such a deprotonation leads to binding of the CD_3O^- alkoxide ion acting as recyclization initiator, and consequently to dying out of the rearrangement. At the same time the addition of a new portion of CD_3ONa (above the equimolar amount) enables completion of the rearrangement. It was thereby shown that the course of the rearrangement depends on the amount of nucleophilic reagent. For the progress and the important completion of the recyclization it is necessary that the amount of the nucleophilic reagent exceeds the molar quantity of the pyrimidinium salt.

On subsequent (after recyclization) recording of the ^1H NMR spectra of the same sample we observed a gradual reduction (in the first 45-60 min) and then complete disappearance of the signals of the methyl group protons (4- and 6-CH_3 of pyridine **4**). This is probably linked with basic deuterium exchange of protons. It is necessary to stress that we recorded no deuterium exchange of the 5-H proton (of the pyridine nucleus) or of the N-methyl group protons. There are literature data on basic deuterium exchange of protons of pyrimidine and pyridine nuclei [6]. Previously we noted deuterium exchange for protons in pyrimidine derivatives [7,8] and considered that it might be an actual process of nucleophilic rearrangement. In the case examined in the present paper, due to the rapid course of the rearrangement (which was also confirmed by NMR spectra), basic exchange of protons occurs after completion of the recyclization and consequently does not hinder it and may not compete with it. It occurs after completion of the rearrangement and consequently is only noticed in the rearrangement product.



EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Varian Mercury 300 (300 MHz) spectrometer in the Center for Investigation of Molecular Structure, National Academy of Sciences (NAN) of Armenia (program US CRDF RESC 17-5). The mass spectra were recorded on a chromato-mass spectrometer (HP 6890 Series Gas Chromatograph, HP 5973 Mass Selective Detector), obtained with grant AR1-991 US CRDF. Silufol UV 254 plates were used for TLC, visualizing with iodine vapor and Ehrlich's reagent. Preparative separation was carried out by column chromatography on silica gel (Silicagel L 5/40 μm).

2-(Cyanomethyl)-4,6-dimethylpyrimidine (2). A mixture of amide **1** [5] (10.0 g, 0.06 mol) and P_2O_5 (7.1 g, 0.05 mol) was carefully heated for 10-15 min until homogeneous. After cooling the reaction mixture was transferred to a sublimation apparatus and sublimed at 85-100°C (3-5 mm Hg). Nitrile **2** (2.9 g, 33%) was obtained having mp 75-77°C, R_f 0.47 (Silufol UV 254, benzene–acetone, 3:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.48 (6H, s, 4- and 6-CH_3); 3.99 (2H, s, CH_2); 6.98 (1H, s, 5-H). Found, %: C 65.59; H 6.45; N 28.39. $C_8H_9N_3$. Calculated, %: C 65.29; H 6.16; N 28.55.

2-(Cyanomethyl)-1,4,6-trimethylpyrimidinium Iodide (3). A solution of nitrile **2** (1.47 g, 0.01 mol) in MeI (5 ml, 11.36 g, 8-fold excess) was heated in a sealed glass ampul at 90-100°C for 10 h. The resulting solid was filtered off, washed with a small quantity of hexane, and air dried. Salt **3** (1.76 g, 61%) was obtained having mp 158-160°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.78 (3H, s, 4 or 6-CH_3); 2.85 (3H, s, 6 or 4-CH_3); 4.08 (3H, s, N-CH_3); 5.03 (2H, s, CH_2); 8.19 (1H, s, 5-H).

Rearrangement of 2-(Cyanomethyl)-1,4,6-trimethylpyrimidinium Iodide (3) into 4,6-Dimethyl-2-methylaminonicotinonitrile (4). A. Iodide **3** (0.6 g, 2.0 mmol) was dissolved in an alcoholic solution of sodium ethylate [sodium (0.06 g, 2.7 mmol) in EtOH (10 ml)] and the solution was left at room temperature for 30 min. After neutralizing with an alcoholic solution of HCl, the precipitated salt was filtered off. A portion of the solvent was removed, the precipitated solid was filtered off, and washed with hexane. The yield of pyridine **4** was 0.3 g (90%) of mp 216-217°C, R_f 0.3 (benzene–acetone, 3:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.21 (3H, s, 4 or 6-CH_3); 2.25 (3H, s, 6 or 4-CH_3); 3.1 (3H, s, N-CH_3); 3.6 (1H, s, NH); 5.71 (1H, s, 5-H). Mass spectrum, *m/z* (I_{rel}, %): 162 (7), 161 (100) $[M]^+$, 121 (13), 120 (21), 119 (20), 108 (9), 105 (9), 94 (10), 93 (12), 81 (10), 80 (47), 79 (9), 66 (15), 55 (18), 53 (12). Found, %: C 67.34; H 6.59; N 25.98. $C_9H_{11}N_3$. Calculated, %: C 67.06; H 6.87; N 26.07.

B. A solution of iodide **3** (0.5 g, 1.7 mmol) in 15% ethanolic methylamine solution (5 ml) was heated in a sealed ampul at 90-100°C for 10 h. The resulting solid was filtered off, dried, and recrystallized from hexane–acetone, 5:1. The yield of pyridine **4** was 0.16 g (58%). After removing the solvent from the filtrate and separation of the residue on a column (silicagel L 5/40, benzene–acetone 3:1), further compound **4** (0.04 g, 14%) and pyrimidine **2** (0.025 g, 10%) were obtained. Mass spectrum, *m/z* 161.

C. A mixture of iodide **3** (0.6 g, 2 mmol) and an alcoholic solution (10 ml) of aminoacid ethyl ester (6-8 mmol) was heated for 15 h at 90-100°C in a sealed glass ampule. The ethanol was removed, and the residue was washed with hot hexane. After distilling off the hexane the residue was put onto a column (silicagel, acetone–benzene, 2 : 1). Pyridine **4** (0.08 g, 52%) was obtained. Pyrimidine **2** was also isolated (with glycine ester 0.04 g (14%), with β-alanine ester 0.06 g (21%)).

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