VILNIUS UNIVERSITY
INSTITUTE OF CHEMISTRY

Živilė Stankevičiūtė

STUDIES ON THE SYNTHESIS AND CYCLIZATION REACTIONS OF ALKYLATED 5-CYANO-2-METHYLSULFANYL-4(3*H*)-PYRIMIDINONES

Summary of Doctoral dissertation
Physical Sciences, Chemistry (03 P)

Vilnius, 2010

The research has been carried out at the Institute of Chemistry in the period of 2004-2009.

Scientific supervisor:

Prof. habil. dr. Albertas MALINAUSKAS (Institute of Chemistry, Physical sciences, Chemistry – 03P)

Doctoral dissertation is defended at the Evaluation board of Chemistry of Vilnius University:

Chairman:
Habil. dr. Gediminas NIAURA (Institute of Chemistry, Physical sciences, Chemistry – 03P)
Members:
Dr. Žilvinas ANUSEVIČIUS (Institute of Biochemistry, Physical sciences, Biochemistry – 04P)
Doc. dr. Algirdas BRUKŠTUS (Vilnius University, Physical sciences, Chemistry – 03P)
Prof. habil. dr. Narimantas ČĖNAS (Institute of Biochemistry, Physical sciences, Biochemistry – 04P)
Dr. Rita BUTKIENĖ (Institute of Chemistry, Physical sciences, Chemistry – 03P)

Official Opponents:
Habil. dr. Linas LABANAUSKAS (Institute of Chemistry, Physical sciences, Chemistry – 03P)
Dr. Jonas ŠARLAUSKAS (Institute of Biochemistry, Physical sciences, Biochemistry – 04P)

The official discussion will be held on May 14, 2010, at the 12 a.m. at the open meeting of the Evaluation board at the Assembly Hall of the Institute of Chemistry.
Adress: A. Goštauto 9, LT-01108, Vilnius, Lithuania

The summary of the doctoral dissertation was mailed on April 13, 2010.
The doctoral dissertation is available at the Library of Institute of Chemistry and at the Library of Vilnius University.

VILNIAUS UNIVERSITETAS
CHEMIJOS INSTITUTAS

Živilė Stankevičiūtė

ALKILINTŲ 5-CIAN-2-METILSULFANIL-4(3*H*)-PIRIMIDINONŲ SINTEZĖS IR CIKLIZACIJOS REAKCIJŲ TYRIMAS

Daktaro disertacijos santrauka
Fiziniai mokslai, chemija (03 P)

Vilnius, 2010

Disertacija rengta 2004–2009 metais Chemijos institute

Mokslinis vadovas:

Prof. habil. dr. Albertas MALINAUSKAS (Chemijos institutas, fiziniai mokslai, chemija – 03 P)

Disertacija ginama Vilniaus universiteto Chemijos mokslo krypties taryboje:

Habil. dr. Gediminas NIAURA (Chemijos institutas, fiziniai mokslai, chemija - 03 P) – pirmininkas
Dr. Žilvinas ANUSEVIČIUS (Biochemijos institutas, fiziniai mokslai, biochemija – 04P)
Doc. dr. Algirdas BRUKŠTUS (Vilniaus universitetas, fiziniai mokslai, chemija – 03P)
Prof. habil. dr. Narimantas ČĖNAS (Biochemijos institutas, fiziniai mokslai, biochemija – 04P)
Dr. Rita BUTKIENĖ (Chemijos institutas, fiziniai mokslai, chemija - 03 P)

Oficialieji oponentai:

Habil. dr. Linas LABANAUSKAS (Chemijos institutas, fiziniai mokslai, chemija – 03P)
Dr. Jonas ŠARLAUSKAS (Biochemijos institutas, fiziniai mokslai, biochemija – 04P)

Disertacija bus ginama viešame Chemijos mokslo krypties tarybos posėdyje 2010 m. gegužės 14 d. 12 val. Chemijos instituto aktų salėje
Adresas: Goštauto 9, LT-2600 Vilnius, Lietuva
Disertacijos santrauka išsiuntinėta 2010 m. balandžio 13 d.
Disertaciją galima peržiūrėti Chemijos instituto ir Vilniaus Universiteto bibliotekose

INTRODUCTION

Pyrimidine derivatives are important group of heterocyclic compounds on theoretical and practical point of view. Heterocyclic systems containing a pyrimidine ring include biological active and for vital functions important compounds. Some of the more important pyrimidine compounds are pyrimidinones. Treatment with alkylating agents, pyrimidinones yielded *N*- and/or *O*-alkylated derivatives. Biological activity and other valuable properties of substituted pyrimidine derivatives stimulated the development of methods for the synthesis of effective and less-toxic substances.

In reactions with electrophilic agents tridentate 4(3*H*)-pyrimidinone anion compose *O*-, N_1- and N_3-alkylated isomers. Direction and selectivity in the alkylation of tridentate 4(3*H*)-pyrimidinone anions are influenced by a number of factors such as the nature of anion, the counter-ion, the alkylating agent, the leaving group, the temperature and the solvent. The alkylated 4(3*H*)-pyrimidinones are valued not only for their chemistry, but also for many important biological properties.

5-Cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone was chosen for experimental work because of its important substitutes for the further transformation. It was obtained on intramolecular cyclization of ethyl (*E*)-2-cyano-3-(*S*-methylisothioureido)-2-propenoate.

We have found that treatment of 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone with the 4-substituted ω-bromoacetophenones readily gives all three *O*-, N_1- and N_3-alkylated isomers. It has been investigated basic cyclization and functionalisation reactions of *O*-alkylated derivatives into 5-aminofuro[2,3-*d*]pyrimidines.

The goal of the work:

To investigate transformation of ethyl (*E*)-2-cyano-3-(*S*-methylisothioureido)-2-propenoate in to 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone, to investigate its *O*- and *N*-alkylation with 4-substituted *ω*-bromoacetophenones, cyclization and functionalisation reactions of *O*-alkylated derivatives.

The tasks of the work:

1. To synthesize ethyl (*E*)-2-cyano-3-(*S*-methylisothioureido)-2-propenoate and investigate its transformations in acidic and alkaline media and to determine optimal conditions for synthesis of 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone.

2. To investigate alkylation of 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone with 4-substituted *ω*-bromoacetophenones and to determine conditions and influence of aromatic ring substitute for *O*-, N_1- and N_3-alkylated products distribution.
3. To investigate cyclization conditions of *O*-alkylated isomers – 4-(4′-*R*-phenacyloxy)-2-methylsulfanylpyrimidin-5-carbonitriles – for synthesis of furo[2,3-*d*]pyrimidines.
4. To investigate functionalization reactions (acetylation, hydrolysis, hydrazinolysis and oxidation) of synthesized 5-amino-6--(4`-*R*-benzoyl)-2-methylsulfanylfuro[2,3-*d*]pyrimidines.

Scientific novelty and practical value of the work.

It was refilled data about transformation of ethyl (*E*)-2-cyano-3-(*S*-methylisothioureido)-2-propenoate in acidic and alkaline media. It was found that boiling in glacial acetic acid proceeds selectively and leads to formation of ethyl 4-amino-2-methylsulfanylpyrimidine-5-carboxylate, while ring closure in alkaline media gives rise to a mixture of 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone (major product), small amounts of ethyl 4-amino-2-methylsulfanylpyrimidine-5-carboxylate and uncyclisized products of hydrolysis – ethyl 2-cyano-3-ureido-2-propenoates, separated as individual compounds. It was investigated alkylation of tridentate 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone with 4-substituted *ω*-bromoacetophenones in the presence of potassium carbonate and catalytic amount of potassium iodide in boiling acetonitrile. It was determined that the proportion of *O*-, N_1- and N_3-alkylated products varied depending on the nature of substitute on the aromatic ring 4-position. For the first time *O*-, N_1- and N_3-alkylated isomers were isolated from alkylation mixture. The main reaction product is the *O*-alkylated isomer with the N_3- and N_1-alkylation products respectively separated as minor components by fractional crystallization. It has been proposed a novel method for the synthesis of furo[2,3-*d*]pyrimidines by Thorpe-Ziegler condensation reaction of *O*-alkylated pyrimidinones. The synthesized compounds could be perspective analogues of the known pharmaceutical and agrochemical agents.

Approbation of the dissertation. Three publications have been published in the international scientific journals on the theme of dissertation. The research results have been presented at 4 Lithuanian national and 1 international scientific conferences.

1. Experimental

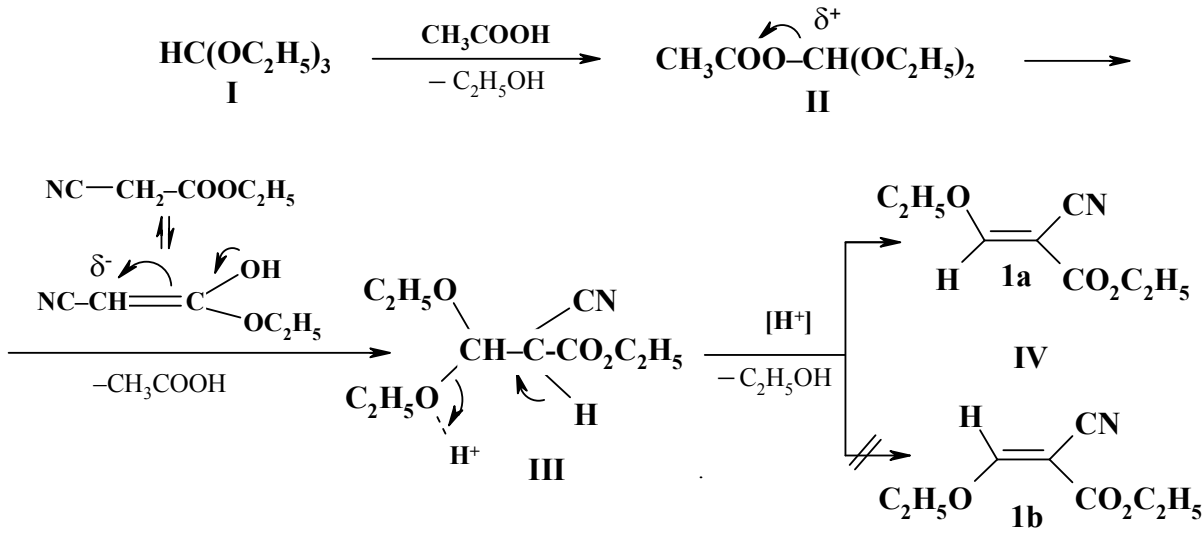
IR spectra were taken on a Perkin-Elmer BX II FT-IR spectrophotometer for KBr tablets and ^{1}H and ^{13}C NMR spectra on a Varian INOVA spectrometer (300 and 75 MHz respectively) using residual signals of DMSO-d_6 (2.52 and 40.21 ppm) or $CDCl_3$ signals (7.29 and 77.30 ppm) as internal standard. Monitoring of the reaction course and the purity of the compounds prepared was carried out by TLC on Sigma-Aldrich Silica Gel 60 F254 glass plates and were revealed using UV light.

2. RESULTS AND DISCUSSION

2.1 Synthesis of 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone

Ethyl 2-cyano-3-ethoxy-2-propenoate (**1**) was chosen as the starting compound. This is obtained by condensation of ethyl cyanoacetate with ethylorthoformate in the presence of glacial acetic acid:

Scheme 1



According to the general literature of orthoesters, this reaction, probably, involves a three-step mechanism: the first step is transesterification of ethylorthoformate (I), the second step – interaction of activated diethoxymethylacetate II with enolic form of ethyl cyanoacetate and finally (third step) obtained adduct III transformation to ester **1** (IV) catalysed by glacial acetic acid.

Synthetic ethyl 2-cyano-3-ethoxypropenoate **1** seemed to contain only one (*E*)-isomer **1a**, since its NMR spectrum in $CDCl_3$ or DMSO-d_6 displayed one single H-3 olefinic proton signal at 8.03 (**Fig. 1**) or 8.42 ppm respectively. The downfield shift of H-3 olefinic proton in DMSO-d_6 ($\Delta\delta \approx 0.4$ ppm) is due to the formation of hydrogen bond with the solvent.

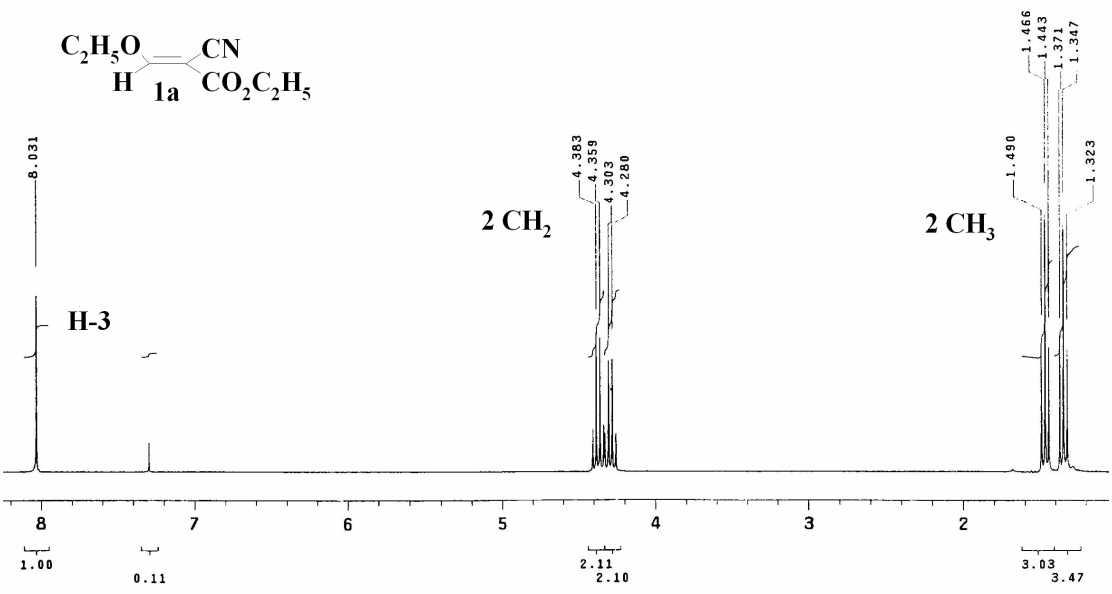


Fig. 1 ^{1}H NMR spectra of ethyl ester **1a** in $CDCl_3$

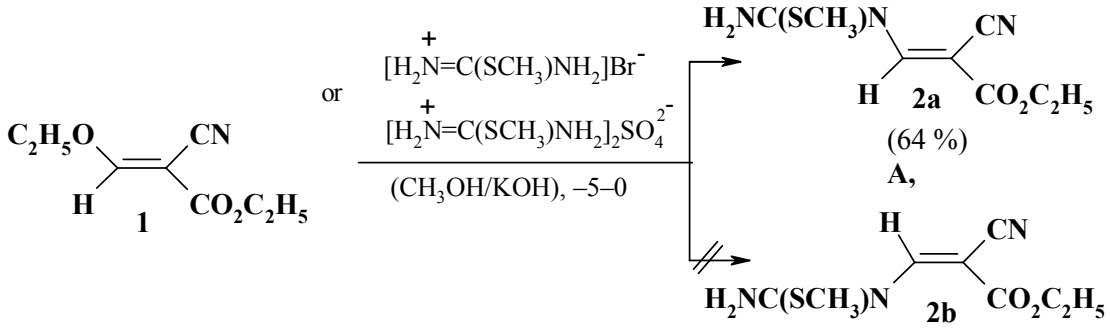
(*E*)-Izomer **1a** (olefinic proton signal at 8.00 ppm) is thermodynamically more stable, and (*Z*)-isomer **1b** (olefinic proton signal at 7.40 ppm) could be detected only by NMR spectra after the irradiation of a chloroform solution with a high-pressure mercury arc, because it isomerizes to the more stable **1a** form during the isolation process. The NMR spectrum in $CDCl_3$ of lower homolog ethyl 2-cyano-3-methoxypropenoate displayed olefinic proton signal at 7.95 ppm, which is close to the one observed for the more stable (*E*)-isomer of the ethoxy-compound **1a**. Unstable isomer of ethyl (*Z*)-2-cyano-3-methoxypropenoate showed an olefinic proton resonance signal at 7.35 ppm.

β-Alkoxyenoates and related compounds like the 3-(dimethylamino)-2-propenoates and 3-halo-2-propenoates undergo substitution reactions with various anionic and uncharged nucleophiles by an addition-elimination S_NVin mechanism. Depending upon the nature of the nucleophile, complete stereoconvergence, or complete or partial retention of the configuration of the double bond has been observed. In cases of *β*-haloenoates elimination of the halogen atom apparently occurred in a rotamer of the

enolate adduct, which would give the more stable product – *trans*-isomer, although thermodynamic control could be involved as well. In cases of *β*-alkoxyenoates, the first step is nucleophilic substitution of the alkoxy group, followed by cyclization.

Ethyl *(E)*-2-cyano-3-(*S*-methylisothioureido)-2-propenoate (**2a**), containing isothioureido-moiety, was synthesized from (*E*)-ethyl 2-cyano-3-ethoxypropenoate (**1a**) and *S*-methylisothiuronium bromide or sulfate in moderate yield:

Scheme 2



In this case S_NVin reaction proceeds with complete retention of the configuration. Steric considerations dictate that *(E)*-isomer **2a** should be more stable than (*Z*)-isomer **2b** as the trigonal carbalkoxy group has larger steric requirements than the linear nitrile group**.** This conclusion is substantiated by chemical-shifts of vinylic H and carboethoxy group: no doubling have been observed in different solvents in the ^{1}H NMR spectrum of ethyl propenoate **2a**.

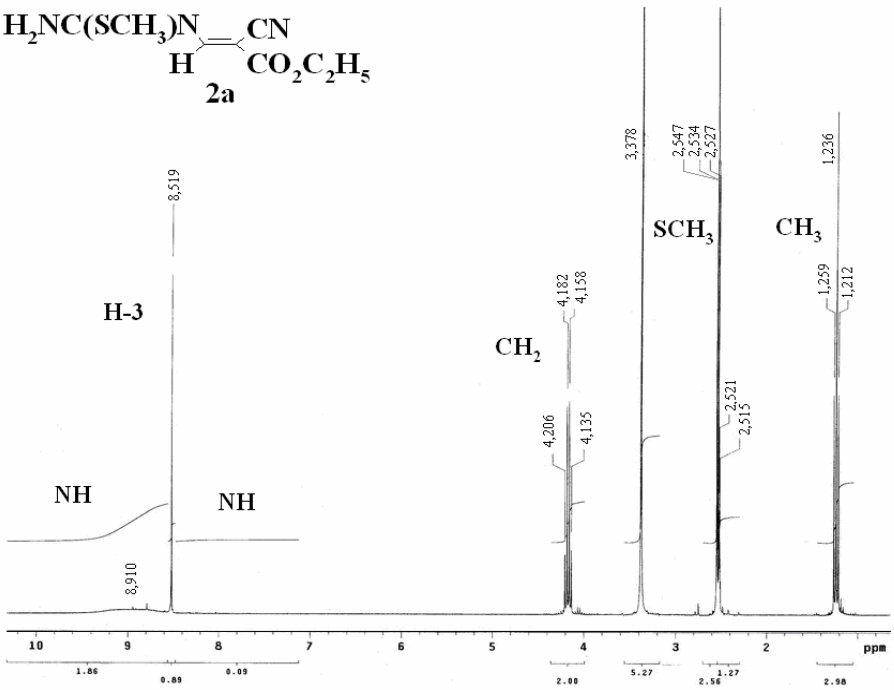


Fig. 2 ^{1}H NMR spectra of ethyl ester **2a** in DMSO-d_6

Such configuration of the prevailing (*E*)-isomer supports data of methyl 3-dimethylamino-2-cyano-2-propenoate (only one =CH signal at 7.70 ppm in $CDCl_3$) and related compounds.

It was found that cyclization of 3-isothioureido-derivative **2a** is significantly influenced by media of reaction. Cyclization in boiling glacial acetic acid leads to selectively formation of ethyl 4-amino-2-methylsulfanylpyrimidine-5-carboxylate (**3**).

Ring closure in alkaline media (0.5 M NaOH or 0.5 M KOH) give rise to a mixture of 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone (**4c,** major product), small amount of compound **3** and uncyclisized products of hydrolysis (*E*)- and (*Z*)-isomers of ethyl 2-cyano-3-ureido-2-propenoate **5a,b** (data of the product distribution on base–catalyzed cyclization is presented in **table 1**). In case of 5 M NaOH (E method) hydrolysis of 2-cyanogroup of compound **2a** was occured and compound **4d** was formed.

The elemental analyses of compounds **5a,b** indicated that they all had the same composition ($C_7H_9N_3O_3$). Their structures were chiefly verified by the following spectral studies: the NMR spectra of the two isomers of **5a,b** show the doublet signal due to the vinyl proton coupled with the adjacent NH proton, and the downfield NH signal attributed to an intramolecular hydrogen bonding between the amino and the ester groups was assigned to that of the (*Z*)-form.

Scheme 3

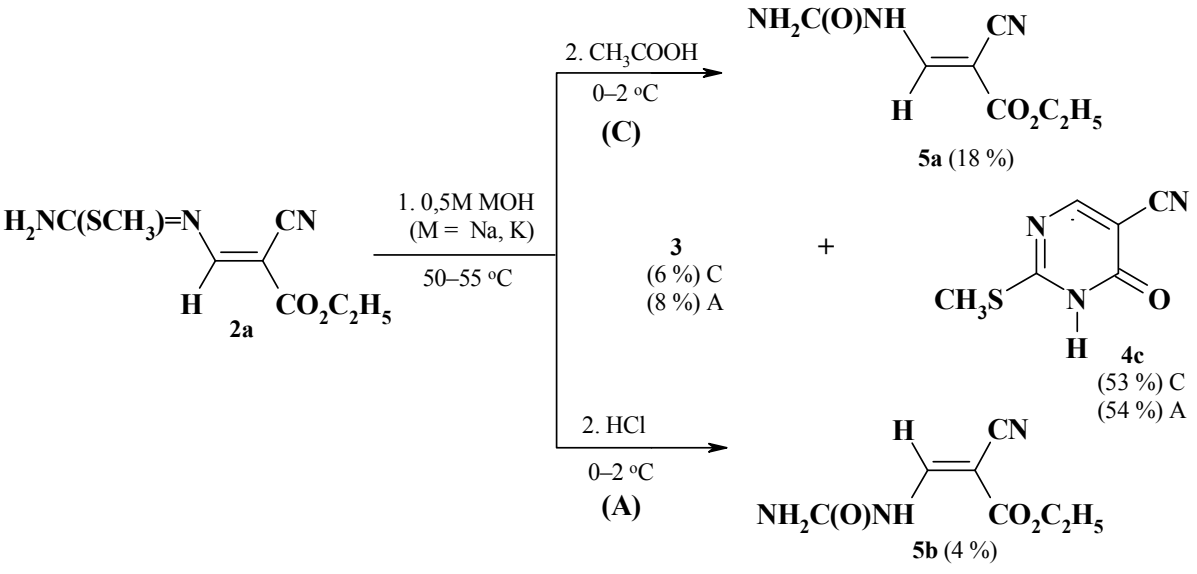


Table 1. Investigation of cyclization of compound **2a**

Method	Reaction conditions					Yield of products, g (%)		
	Amount of ester 2a g (mmol)	Amount of 0.5 M NaOH mL	Time of reaction (min)	Temp °C	Acid	**3**	**4c**	**5a. b**
A	21.3 (100)	213 NaOH	15	50	1 M HCl	1.66 (8)	9.14 (54)	0.90 (4)
B	1.0 (4.7)	10 NaOH	60	16	1 M HCl	0.06 (6)	0.25 (32)	0.18 (21)
C	1.0 (4.7)	10 NaOH	60	18	conc. CH_3COOH	0.06 (6)	0.42 (53)	0.11 (18)
D	29.2 (130)	370 NaOH	15	50–55	1 M HCl	3.57 (12)	8.85 (38)	5.28 (21)
E	2.13 (10)	20 5M NaOH	10	45–50	1 M HCl	0.16 (16)	0.55 **4d**	-
F	1.0 (4.7)	10 KOH	10	50–52	1 M HCl	0.04 (4)	0.25 (32)	0.36 (42)
G	1.0 (4.7)	10 KOH	10	50–53	conc. CH_3COOH	0.03 (3)	0.26 (33)	0.22 (26)
H	2.00 (9.4)	20 NaOH	3	50–55	1 M HCl	0.01 (0.5)	0.09 (6)	0.23 (13)
J	1.0 (4.7)	15 NaOH	120	15	1 M HCl	0.03 (4)	0.29 (45)	0.15 (22)
K	2.00 (9.4)	20 NaOH	140	18	conc. CH_3COOH	0.16 (8)	0.48 (30)	0.49 (28)

It is noteworthy that one of isomer or isomeric mixture of ethyl 2-cyano-3-ureido-2-propenoate (**5,** m. p. 215 °C) was synthesized by C. W. Whitehead and repeated by Ledvina and R.S. Vardanyan et al. from urea, ethyl orthoformate and ethyl cyanoacetate. As noticed (*E*)-isomer was obtained as the sole product. Another synthesis of mixture **5a,b** is presented by treatment of 2-ethoxycarbonyl-3-dimethylaminopropenenitrile with urea. In our work we isolated two isomer **5a** and **5b**, which represent (*E*)- and (*Z*)-isomers (**fig. 3**). By our knowledge the fact about isolation of these isomers were not noticed in literature. (*Z*)- and (*E*)-ethyl 2-cyano-3-ureido-2-propenoates were isolated in different acidity of reaction mixture: (*Z*)-isomer at pH 1 (acidification with hydrochloric acid) and (*E*)-isomer at pH 2-3 (acidification with acetic acid) is significantly influenced by media of reaction.

In ^{1}H NMR spectra for (*E*)-isomer **5a** typical is H-3 signal at 8.41 ppm, analogical signal for (*Z*)-isomer **5b** is observed in a stronger field at 8.11 ppm. NH protons doublet shift for (*E*)-isomer **5a** is at 10.34 ppm, for (*Z*)-isomer **5b** at 10.58 ppm.

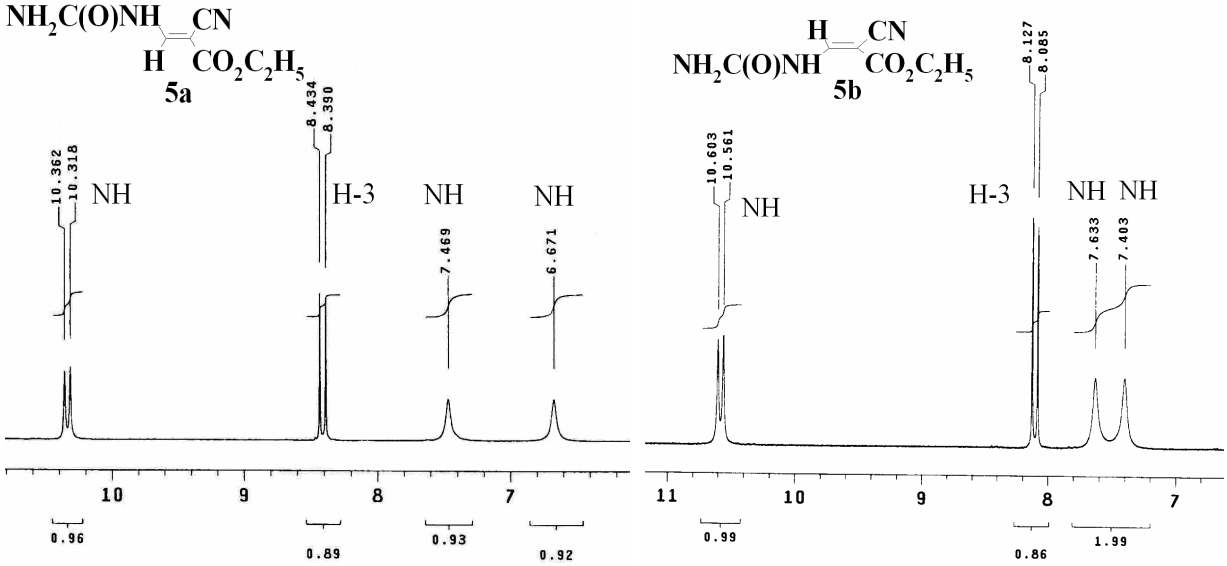
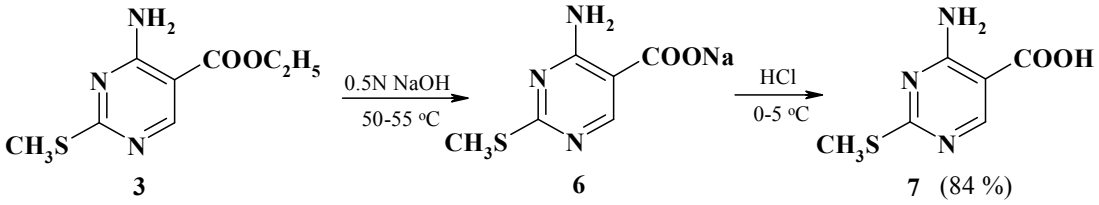


Fig. 3 ^{1}H NMR spectral fragment of compounds **5a,b** in DMSO-d_6

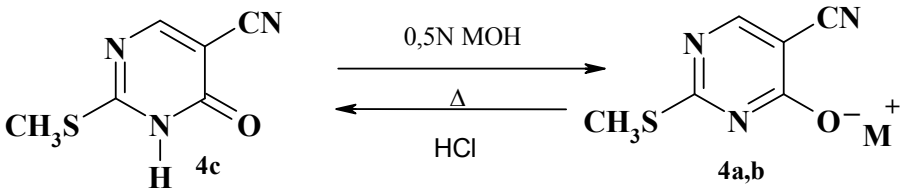
Compounds **3** and **4c** can be converted into corresponding alkali metal salts by treatment with alkali, and substitution products of 2-methylsulfanyl group by hydroxy group or rearrangement products of ethyl pyrimidine-5-carboxylate were not detected. Salt **6** was acidified with HCl acid to give corresponding 4-amino-5-carboxycompound:

Scheme 4



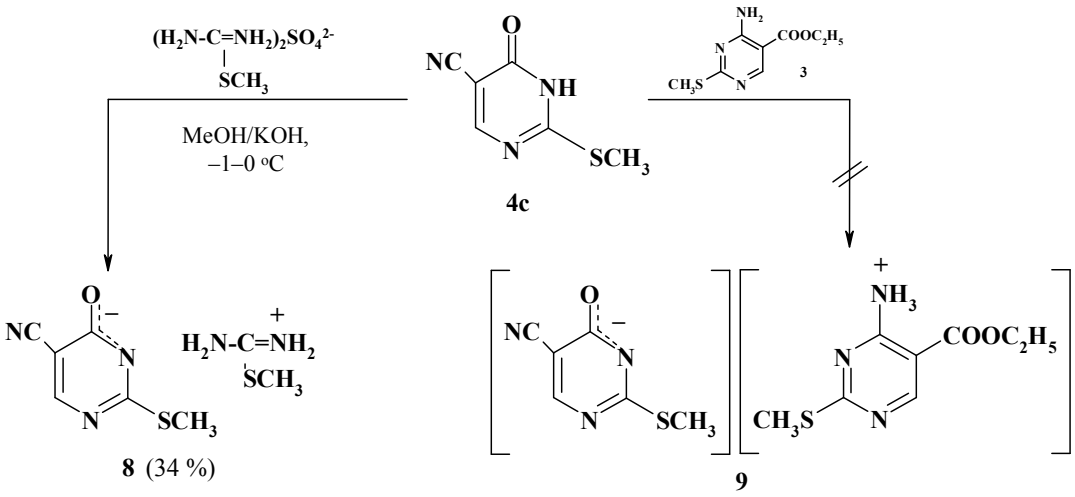
After acidification salts **4a,b** were given starting compound **4c**.

Scheme 5



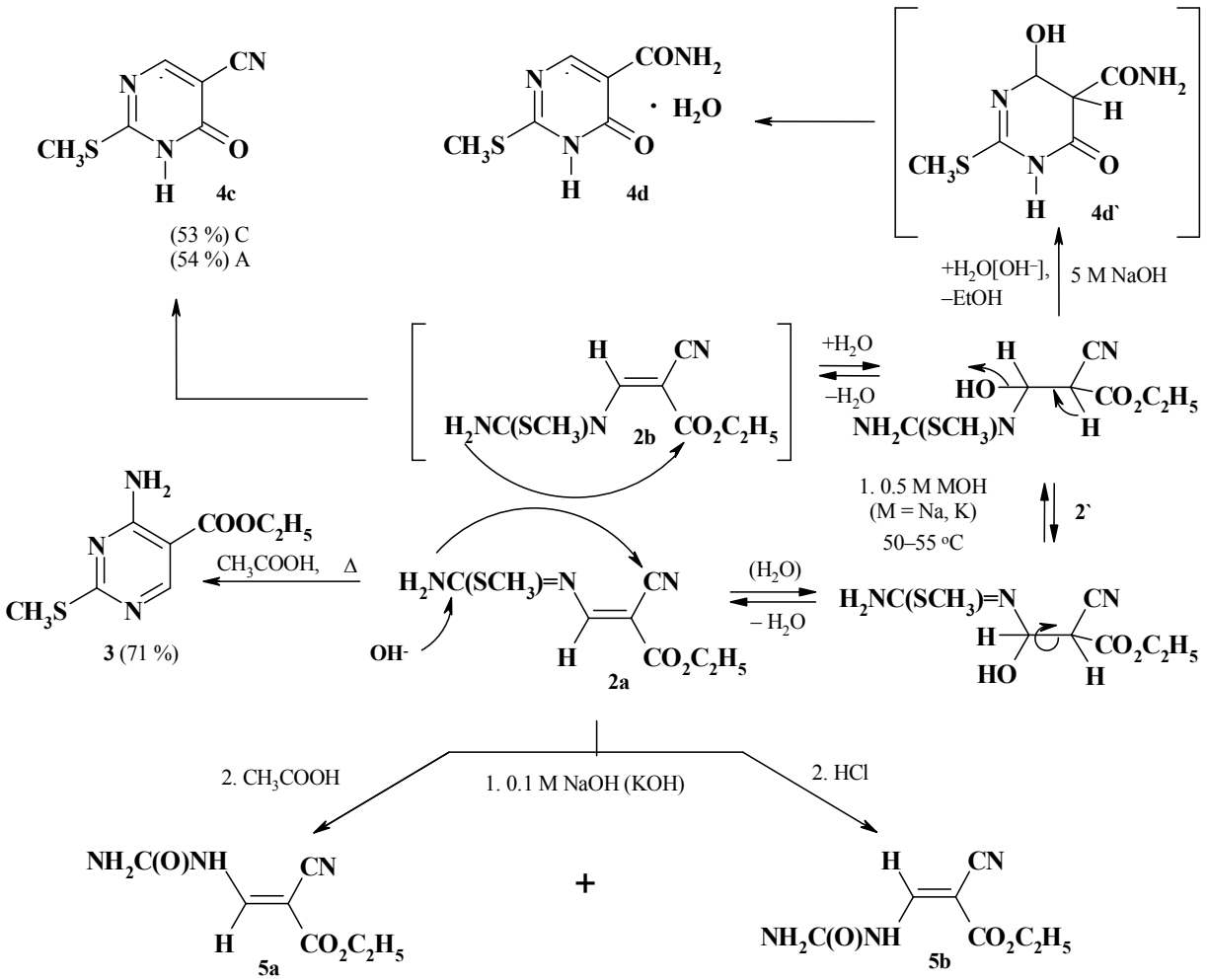
Compound **8** was not detected in cyclization mixture, which was synthesized for structure comparison. Treatment pyrimidinone **4c** with ethylcarboxylate **3**, analogical salt **9** were not formed.

Scheme 6



General transformations of compound **2a** are represented in **scheme 7**.

Scheme 7



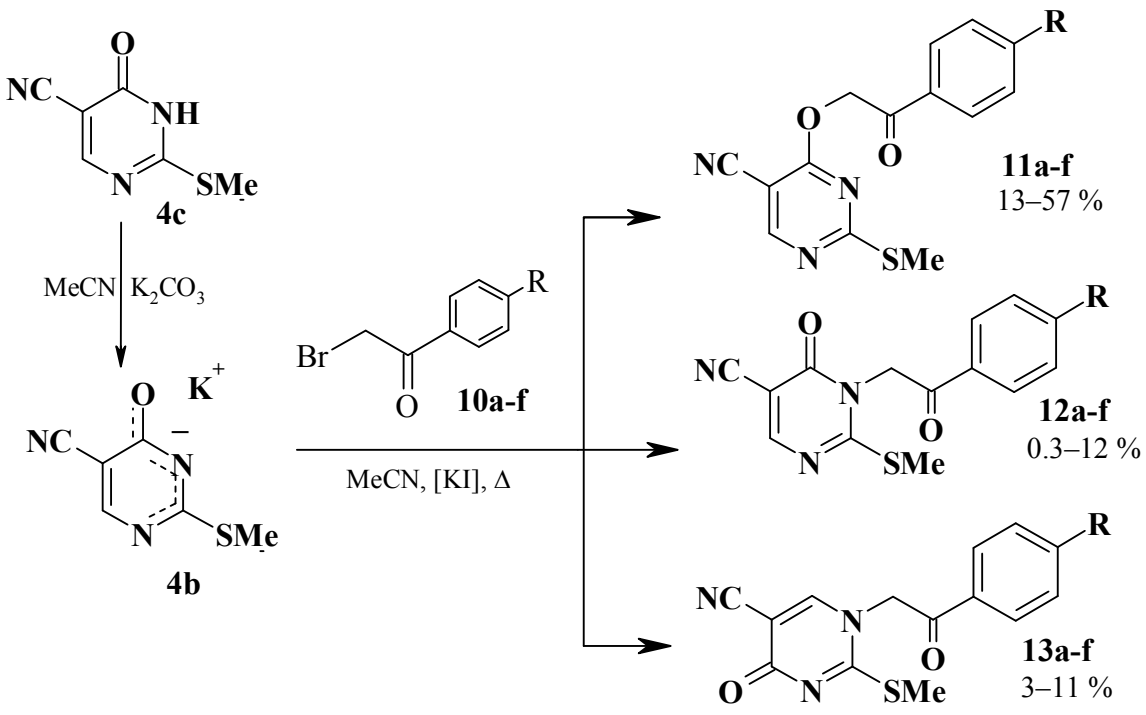
2.2 Alkylation of 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinones

Alkylation of 4(3*H*)-pyrimidinones occurs to give a mixture of N_1-, N_3-, and *O*-alkylation products. Analysis of literature data shows that alkylation with haloacetic esters, chloroacetonitrile, N-benzyl-haloacylamides, 3-bromopropan-1-ol, or *ω*-bromoacetophenone generally gives just the *O*- and/or N_3-alkylation products. To best of our knowledge, N_1-alkylated products were only detected or isolated using alkyl halides or dimethyl sulfate as the alkylating agents. Selectivity in the alkylation of tridentate 4(3*H*)-pyrimidinone anions is influenced by a number of factors such as the nature of anion, the counter-ion, the alkylating agent, the leaving group, the temperature and the solvent.

We have found that treatment of 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone (**4c**) with the 4-substituted *ω*-bromoacetophenones **10a-f** in the presence of potassium carbonate and a catalytic amount of potassium iodide in anhydrous acetonitrile medium readily gives all three *O*-, N_3-, and N_1-alkylation products **11a-f** to **13a-f**. According to ^{1}H NMR spectroscopic data for the reaction mixtures side products are not formed under these conditions.

It was noted that the proportion of *O*-, N_1- and N_3-alkylated products varied depending on the nature of substitute on the aromatic ring 4-position.

Scheme 8



10-13 a R = H, **b** R = CH_3, **c** R = OCH_3,
d R = Cl, **e** R = Br, **f** R = NO_2

The main reaction product is the *O*-alkylated isomer **11a-f** with the N_3- and N_1-alkylation products **12a-f** and **13a-f** respectively separated as minor components by fractional crystallization or by column chromatography (the overall alkylation yield being 44–83 %). Elemental analysis, IR , ^{1}H and ^{13}C NMR spectra for the compounds

prepared were fully in agreement with their structures as alkylated derivatives of the 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone.

^{1}H and ^{13}C NMR spectral characteristics of typical signals of alkylated compounds are presented in **tables 2–3**.

Table 2. ^{1}H NMR some spectral characteristics of compounds **11-13 a-f**

Groups	**11a–f** (X = O)	**12a–f** (X = N_3)	**13a–f** (X = N_1)
SCH_3	2,31–2.33	2.63–2.64	2.50–2.51
XCH_2	5.99–6.11	5.66–5.82	5.69–5.86
6-H	8.93–8.96	8.63–8.69	8.58–8.61

Table 3. ^{13}C NMR some spectral characteristics of compounds **11-13 a-f**

Groups	**11a–f** (X = O)	**12a–f** (X = N_3)	**13a–f** (X = N_1)
SCH_3	14.4	16.0–16.0	15.1–15.1
XCH_2	70.0–70.5	51.4–52.2	58.9–59.5
C6	162.84–162.91	158.84–158.91	166.65
C5	90.91–90.93	96.60–96.66	94.93–95.02
C4	167.3–167.6	170.6–170.7	163.0–163.1
C2	176	161	155

^{1}H NMR spectral fragments of individual compounds **11–13**, essential for its identification, are represented in **fig. 4–5**.

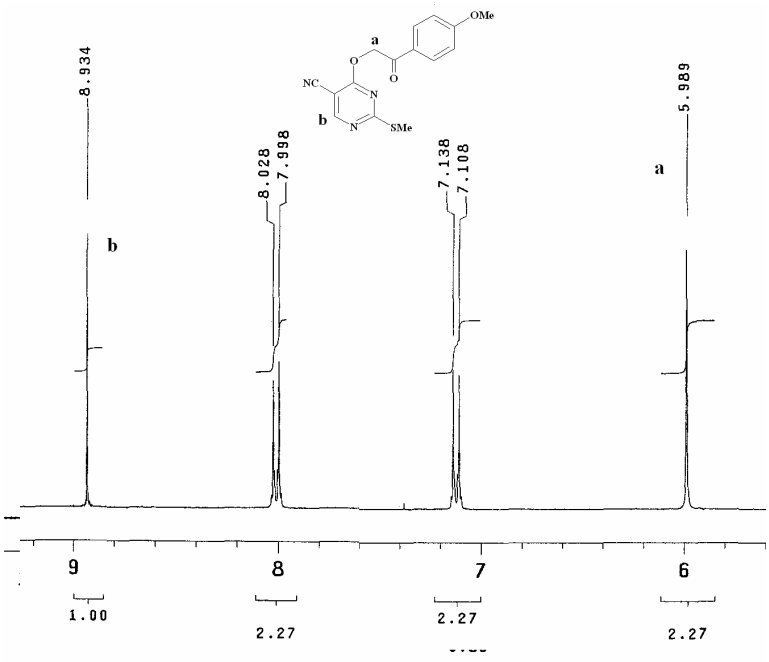


Fig. 4. ^{1}H NMR spectral fragment of compound **11c** in DMSO-d_6

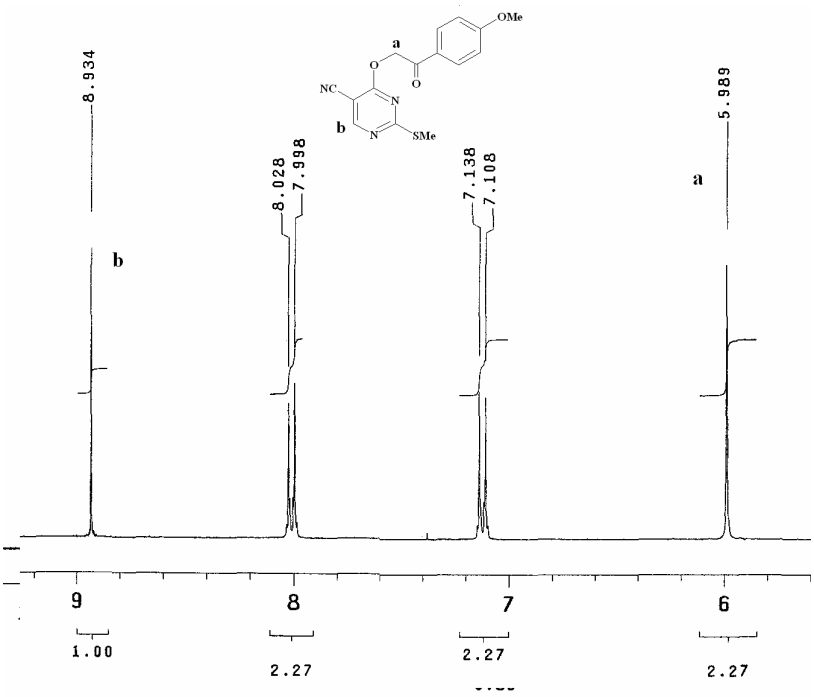


Fig. 5. ^{1}H NMR spectral fragment of compound **12c** in DMSO-d_6

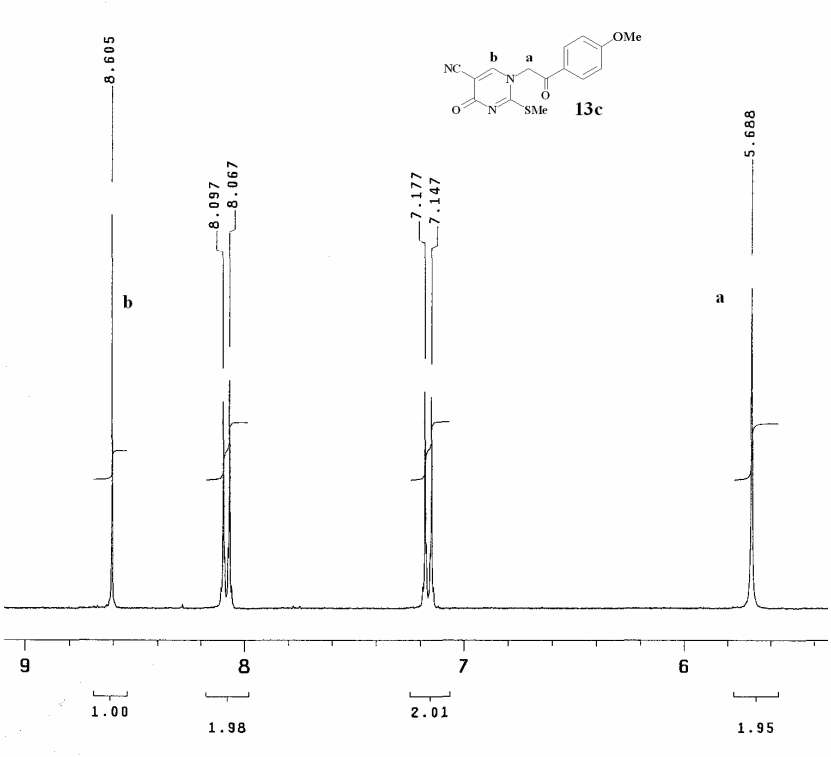


Fig. 6. ^{1}H NMR spectral fragment of compound **13c** in DMSO-d_6

In IR spectrums are observed valence vibrations absorption bands of ν_{CN} and ν_{CO} groups: 2226–2232 and 1686–1705 for *O*-alkylated isomers, 2224–2234, 1690–1698 and 1678–1685 for N_3-isomers, 2226–2229, 1684–1692 and 1652–1623 cm^{-1} for N_1-isomers respectively (**fig. 7–9**).

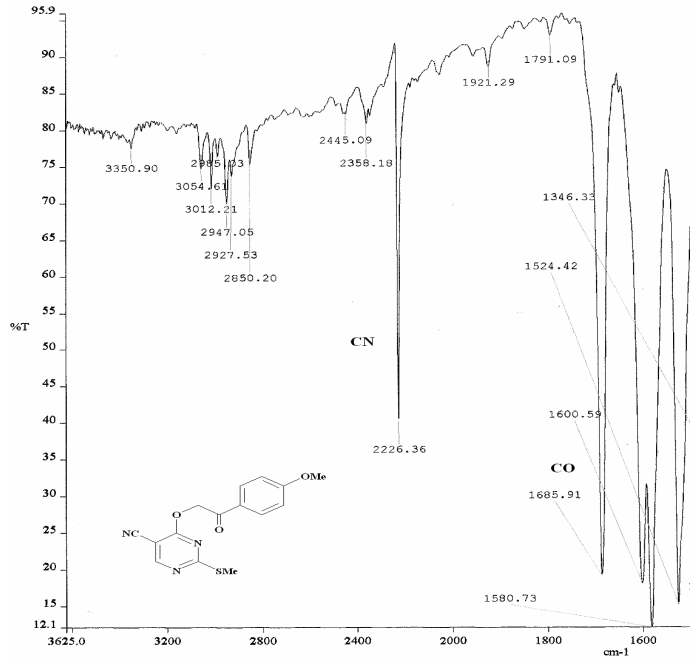


Fig. 7. IR spectral fragment of compound **11c**

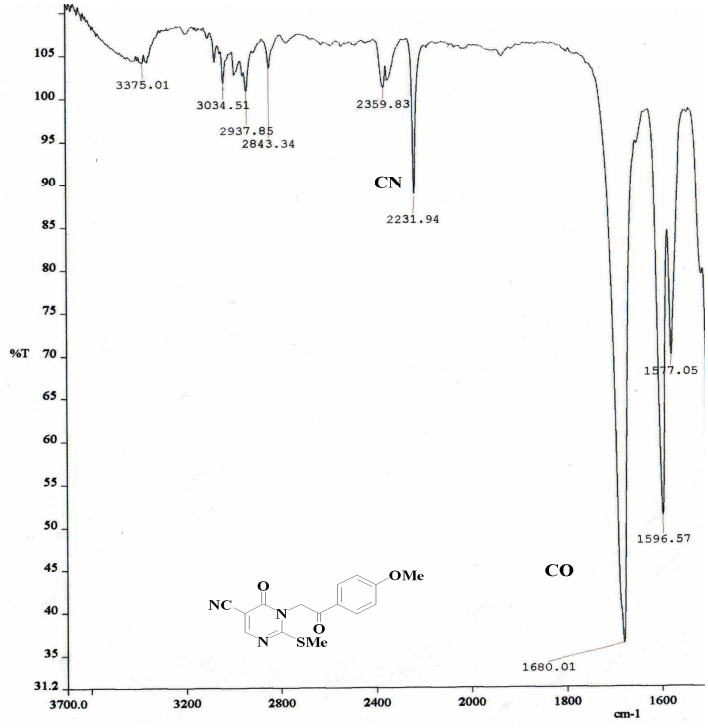


Fig. 8. IR spectral fragment of compound **12c**

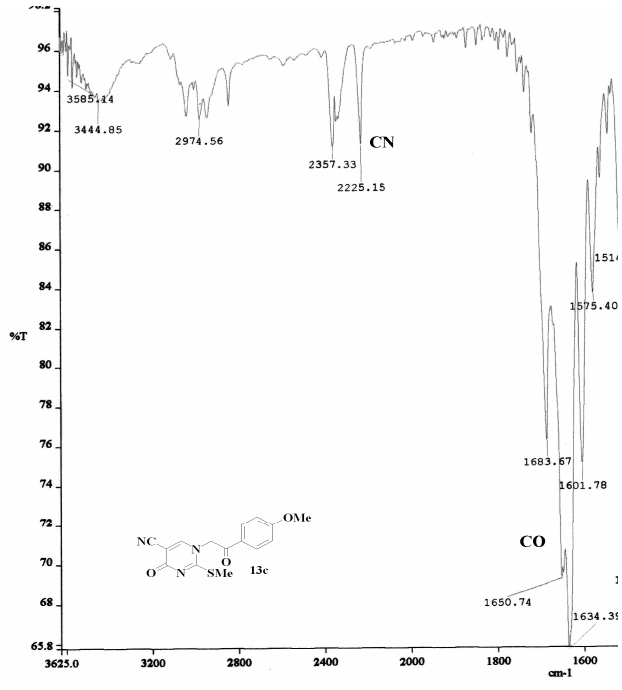


Fig. 9. IR spectral fragment of compound **13c**

The distribution of alkylated compounds **11-13 a-f** in reaction mixtures was determined by ^{1}H NMR method (**table 4**).

Table 4. ^{1}H NMR spectral data of distribution of alkylated compounds **11-13 a-f** in alkylation mixtures

R	XCH_2 proton signals						H–6 proton signals					
	11 (X = O)		**12** (X = N_3)		**13** (X = N_1)		**11**		**12**		**13**	
	ppm	%	ppm	%	ppm	%	ppm	%	ppm	%	ppm	%
a	6.06	82	5.74	8	5.77	10	8.95	79	8.68	8	8.61	13
b	6.01	79	5.69	9	5.72	12	8.94	76	8.67	9	8.61	15
c	5.99	78	5.66	9	5.69	13	8.94	76	8.67	9	8.61	15
d	6.04	81	5.73	11	5.76	8	8.94	80	8.67	10	8.59	10
e	6.04	76	5.77	15	5.77	9	8.95	75	8.68	16	8.59	10
f	6.11	71	5.82	22	5.87	7	8.96	72	8.69	18	8.59	6

In all cases three alkylated compounds are formed and no side products were observed. Ratio of alkylated isomers were appointed by XCH_2-group (X = *O*, N_1, N_3) and H-6 peaks integral intensity of pyrimidine ring accordingly in 5.66–6.11 and 8.59–8.96 ppm. By ^{1}H NMR spectral data, *O*-alkylated isomers **11 a-f** are a major products, N_3- and N_1-alkylated products proportions varied depending on the nature of substitute on the aromatic ring 4-position: electron-donating substitutes (CH_3, OCH_3) gives more N_1-isomers **12 a-f**, the electron-withdrawing substitutes (Cl, Br, NO_2) gives more N_3-isomers **13a-f**.

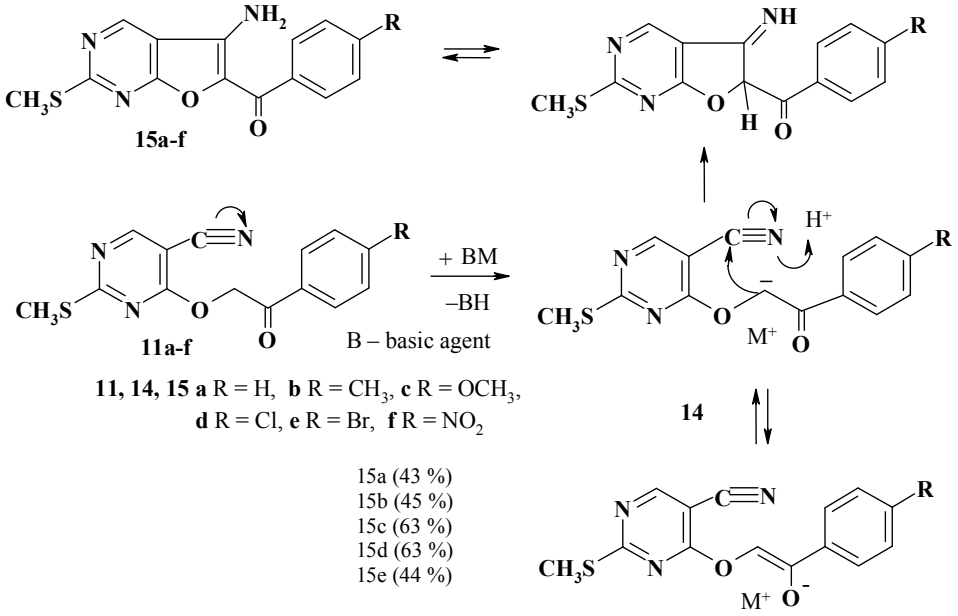
18 alkylated isomers are obtained in alkylation mixtures, 16 of them have been isolated by fractional crystallization and identificated as the individual compounds. R_f value of compounds **11b** and **12b** are very similar and compound **13f** is unstable on isolation conditions.

The alkylated 4(3*H*)-pyrimidinones are valued not only for their chemistry, but also for many important biological properties. *O*-alkylated derivatives display anticancer, antibacterial, antithrombotic, diuretic activities. N_3-alkylated pyrimidinones have also been extensively investigated for their pharmacological uses – some of them are potential analgesic and antiinflammatory, diuretic, hypotensive, calcilytic, herbicidal compounds.

2.3 Cyclization reactions of *O*-alkylated compounds 11a-f

In this work was proposed new synthesis method for furo[2,3-*d*]pyrimidine system synthesis by cyclization of 2-methylsulfanyl-4-[4′-*R*-phenacyloxy]pyrimidine-5-carbonitriles (**11a-f**) under Thorpe-Ziegler basic conditions.

Scheme 9



Pyrimidin-5-carbonitriles **11a-f** have been further transformed into 5-aminofuro[2,3-*d*]pyrimidines by the basic cyclization. While condensations of this sort in pyridine chemistry have been reported previously in the literature, to our knowledge cyclocondensation reaction of 5-cyano-[4(6)-phenacyloxy]pyrimidines to form furo[2,3-*d*]pyrimidines has not been previously reported.

4-Phenacyloxy-2-methylsulfanylpyrimidin-5-carbonitrile **11a** has been choiced for optimal reaction conditions search, results are represented in **table 5**.

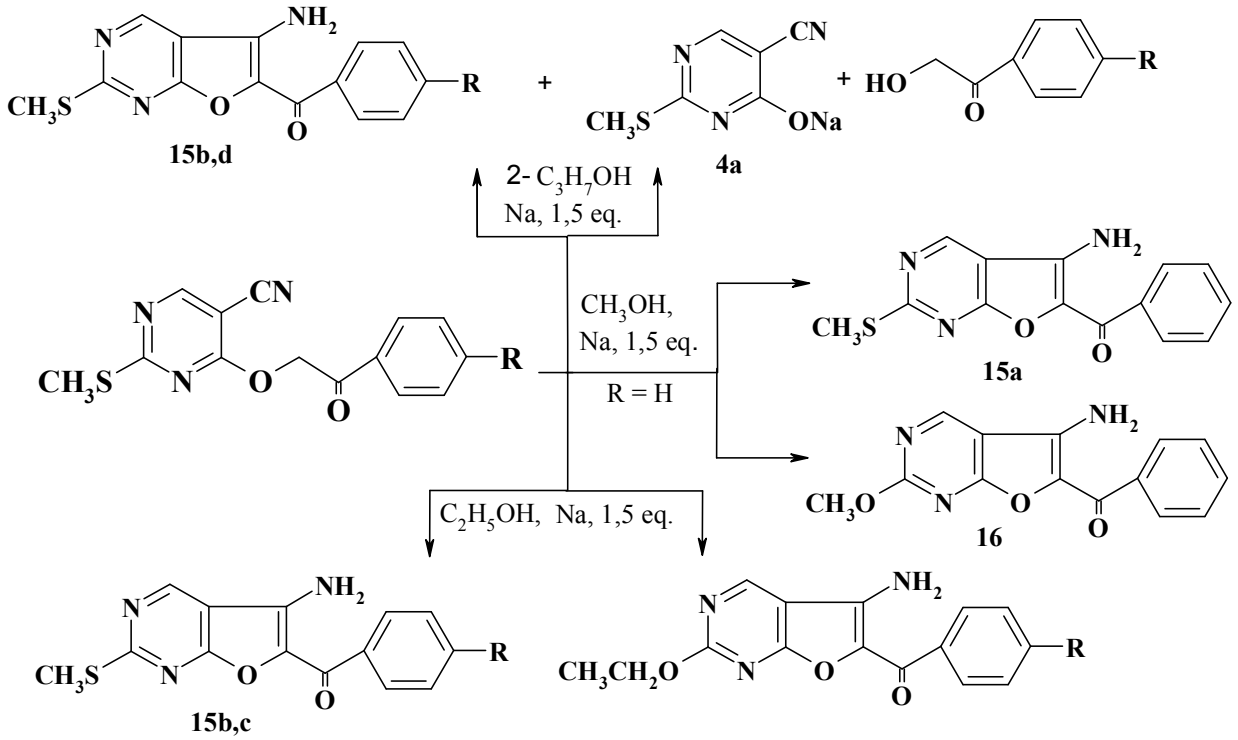
The results show that in aprotic solvents (acetonitrile and benzene) cyclization has been failed. In the system DMF–NaOH are possible hydrolysis reactions, better results obtained in the system C_2H_5OH–C_2H_5ONa.

Table 5. Investigation on cyclization of compound **11a**

No	11a (mmol)	Basic agent (mmol)	Solvent	Temp. °C	Time of reaction (h)	Yield of products, g (%)	mp., °C
A	1	10% KOH (5.30)	DMF–H_2O	16	1 h	0.11 (39 %)	216–218
B	1	10% KOH (5.30)	DMF–H_2O	17	2 min	0.07	153–156/196–201
C	1	10% KOH (5.30)	DMF–H_2O	2–3	1.5 h	0.06	153–158/204–208
D	1	C_2H_5ONa (0.43)	C_2H_5OH	78	2.5 h	0.08	158–160/204–209
E	1	C_2H_5ONa (0.43)	C_2H_5OH	78	10 h	0.09 (32 %)	224–227
F	1	K_2CO_3 (1.00)	CH_3CN	80	22 h	0.06	145–148
G	1	*t*-BuOK (1.00)	C_2H_5OH	78	2.5 h	0.18	148–150
H	0.35	*t*-BuOK (0.35)	CH_3OH	17	45 h	0.04 (32 %)	221–223
J	1	*t*-BuOK (1.00)	*t*-BuOH	82	2 h	0.05	155/208–212
K	1	*t*-BuOK (2.00)	C_6H_6	80	4 h	0.28	301–305
L	0.36	10% NaOH	DMF–H_2O	50–60	18 h	0.03 N_1/0.03 N_2	218–221/215–218
M	0.36	NaH (0.36)	2-PrOH	50–60	6 h	0.05	135–145/195–208
N	0.36	CH_3ONa (1.39)	CH_3OH	65	8 h	0.01	238−241
O	1	C_2H_5ONa (1.00)	C_2H_5OH	78	5 h	0.12 (43 %)	222–225

In reactions with other substitutes (CH_3, OCH_3, Cl, Br, NO_2) different solvents and basic agents have been tested. The influences of solvent and basic agent have been investigated in cyclization reactions with substrates **11b-11f**. Different amount of sodium and various alcohols: methanol, ethanol and 2-propanol have been used. It has been found that with an equivalent amount of sodium some unreacted starting compound observed in reaction mixture. The best yields of 5-amino-6-(4′-*R*-benzoyl)-2-methylsulfanylfuro[2,3-*d*]pyrimidines obtained in ethanol at 1.5 equivalent of sodium ethoxide. The cyclization failed, however, with a substrate **11f**. Cyclization in system CH_3OH–CH_3ONa (2 equivalent or more) leads to displacement reaction of 2-methylsulfanyl- into methoxygroup as byproduct, in this case only product **16** have been isolated.

Scheme 10



The elemental analysis data and spectral characteristics of compounds **15a-f** are in agreement with the proposed structures. In ^{1}H NMR spectra for compounds **15a–e** are typical singlets at 7.67–7.84 ppm of 5-aminogroups and H-4 signals of pyrimidine ring at 9.26–9.27 ppm, then in the starting compounds **11a-f** H-6 signals of pyrimidine ring are observed at 8.93–8.96 ppm. In starting compounds **11a-f** are observed OCH_2-group

signals which disappeared in cyclisized compounds **15a-e** (**fig. 10**). In ^{13}C NMR spectra carbonyl group signal (~131.5 ppm) shifted to the stronger fields in comparison with starting compounds (~90.9 ppm).

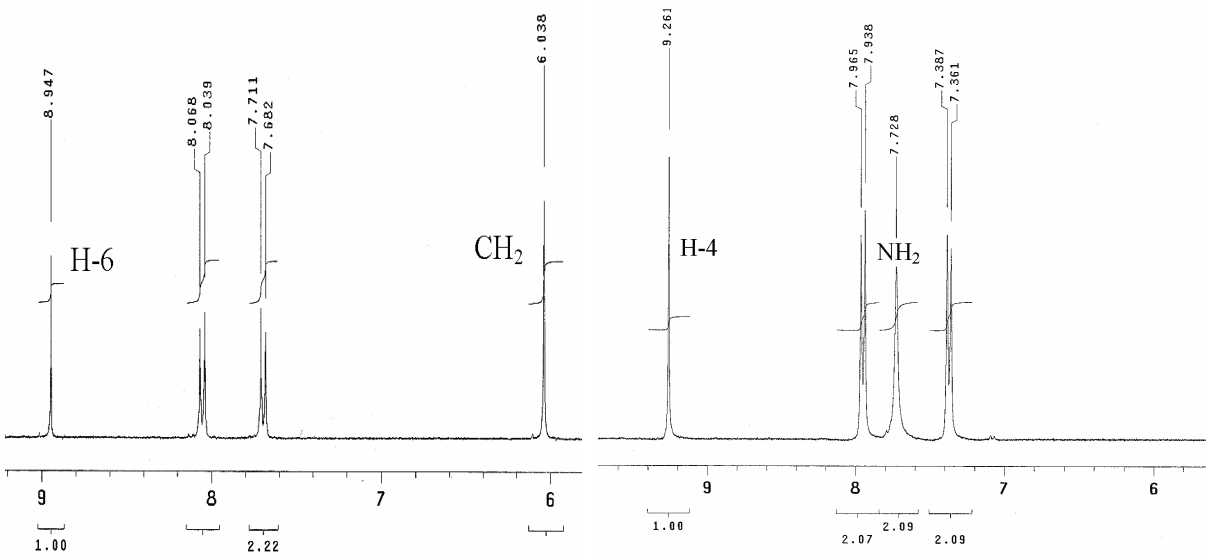


Fig. 10. ^{1}H NMR spectral fragment of compounds **11c** and **15c** in DMSO-d_6

Thus, in IR spectra of **11a-f** are observed the strong absorption band of the CN-group (2225–2232 cm^{-1}). In case of the compounds **15a-e** this peak was not observed. Instead we observed the typical absorptions of the NH_2-group (3413–3193 cm^{-1}).

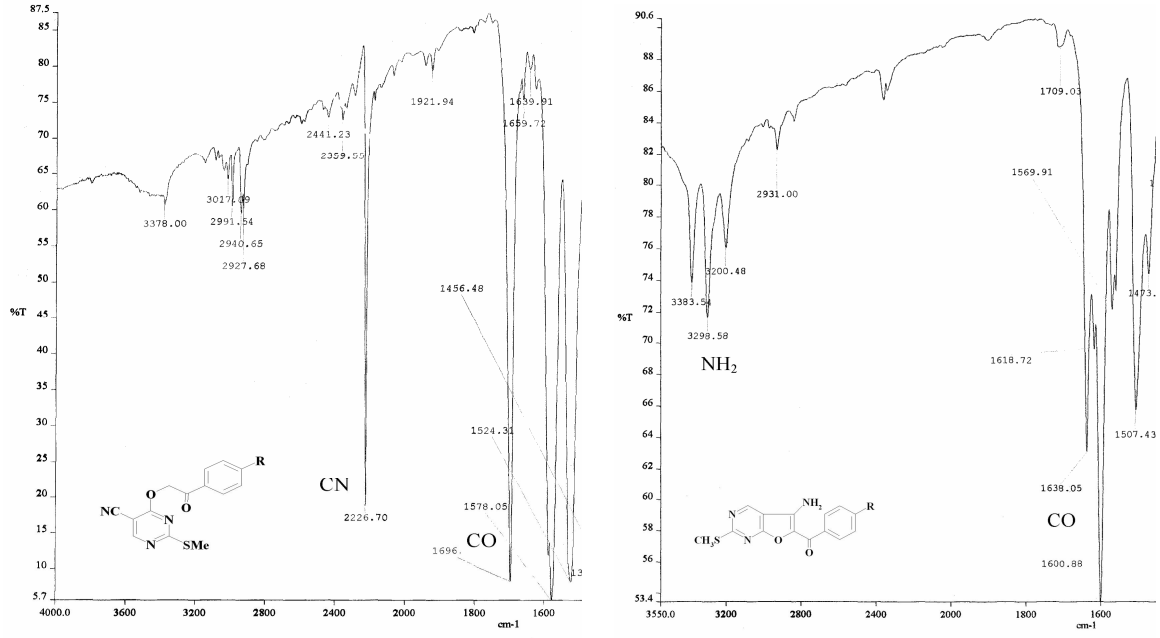
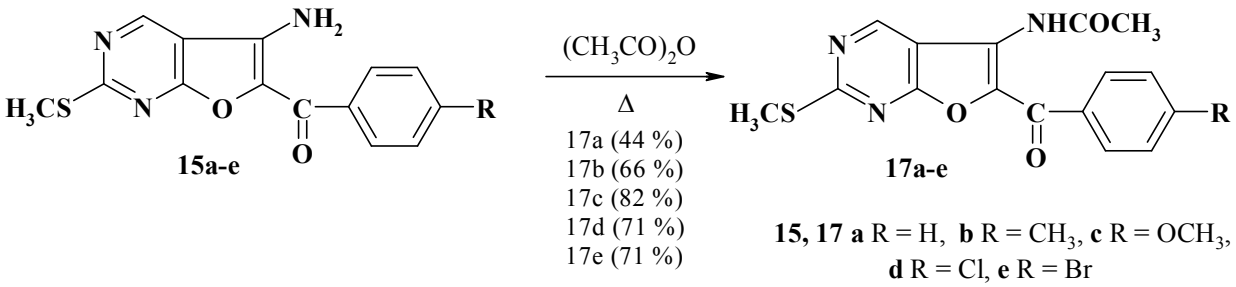


Fig. 11. IR spectral fragment of compounds **11** and **15**

2.4 Chemical properties of furo[2,3-*d*]pyrimidines

Synthesized 5-amino-6-(4′-*R*-benzoyl)-2-methylsulfanylfuro[2,3-*d*]pyrimidines **15a-e** include three functional groups (–NH_2, –C=O and –SCH_3), significant for further transformation reactions. Boiling in acetic anhydride gives monoacetylated compounds **17a-e**:

Scheme 11



Acetylation reaction smoothly proceed with all furo[2,3-*d*]pirimidines **15a-e**. The elemental analysis data and spectral characteristics of compounds **17a-e** are in agreement with the monosubstituted compound structure.

In ^{1}H NMR spectra for compounds **17a–e** are observed new $COCH_3$-group peaks at 2.28–2.31 ppm. In starting compounds **15a–e** NH_2-group signals are observed at 7.66–7.86 ppm and in acetylated compounds NH-group signals resonated at 10.70–10.75 ppm (**fig. 12**).

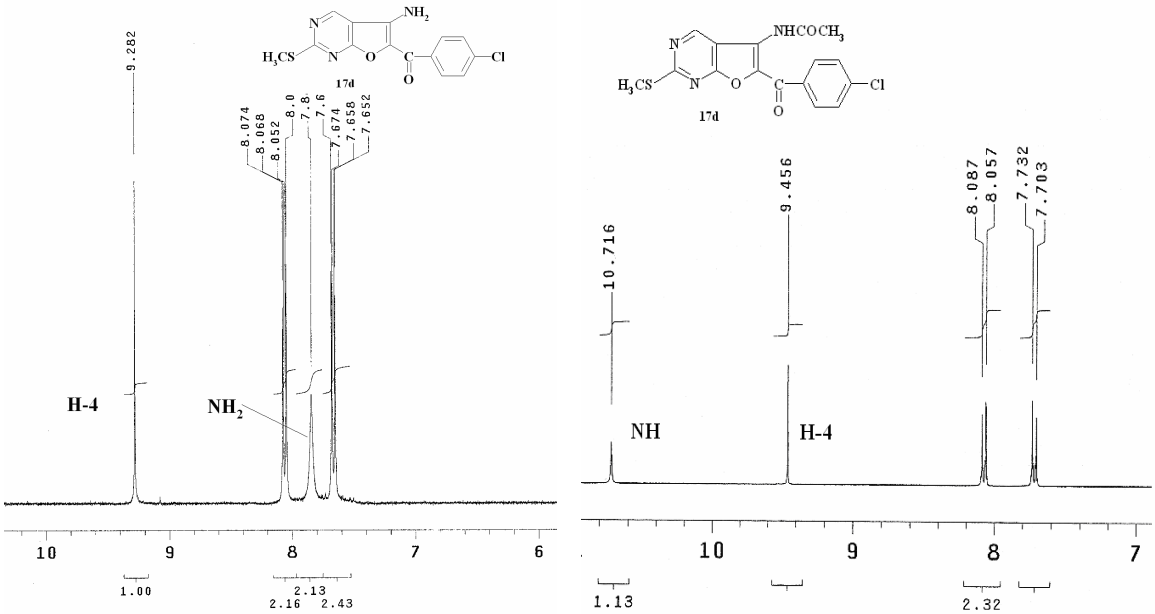
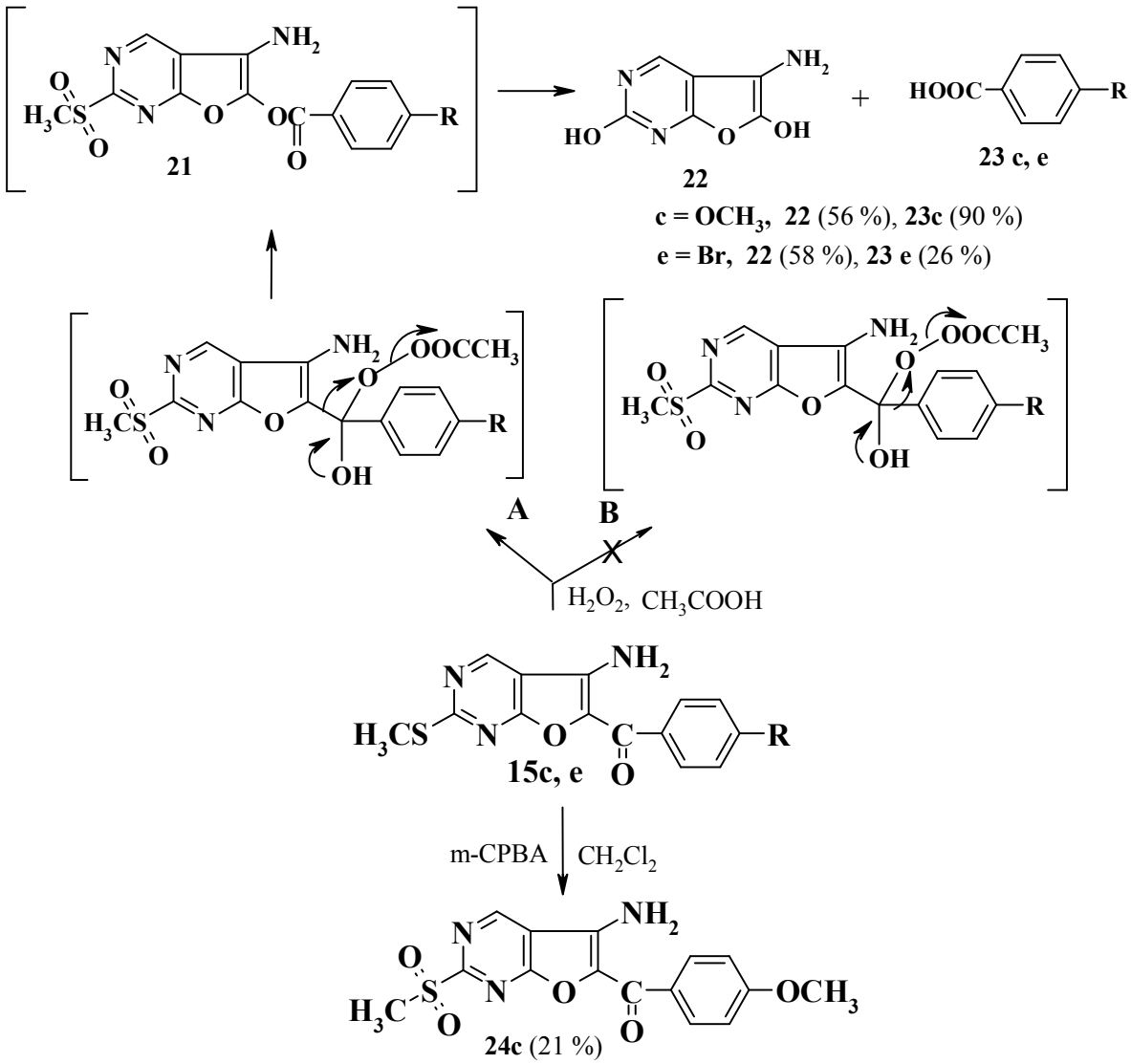


Fig. 12. ^{1}H NMR spectral fragment of compounds **15d** and **17d** in DMSO-d_6

Hydrazinolysis of 1**5b** and hydrolysis reactions of **15 b, d** was occurred for functionalization possibilities of furo[2,3-*d*]pirimidines. Required derivatives were not isolated from reaction mixture.

It was found that 5-amino-6-phenacyl-2-methylsulfanylfuro[2,3-*d*]pyrimidines **15c,e** under oxidative conditions (H_2O_2–acetic acid) cleaved into 5-amino-2,6-dihydroxyfuro[2,3-*d*]pyrimidine (**22**) and corresponding *p*-substituted carboxylic acid **23c,e**. It seems likely that the SCH_3 and CO groups in the starting compounds **15c,e** are oxidized to the methylsulfonyl and ester groups which then are hydrolyzed under these reaction conditions. Treatment **15c** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2 yielded a mixture of oxidative products, only small amount of compound **24c** was isolated from reaction mixture.

Scheme 12



3. CONCLUSIONS

1. Cyclization of ethyl 2-cyano-3-(*S*-methylisothioureido)-2-propenoate under acidic conditions proceeds selectively and leads to formation of ethyl 4-amino-2-methylsulfanylpyrimidine-5-carboxylate while in alkaline media gives rise to a mixture of cyclization and hydrolysis products: 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone, small amounts of 4-amino-2-methylsulfanylpyrimidine-5-carboxylate and (*Z*)- and (*E*)-isomers of ethyl 2-cyano-3-ureido-2-propenoate. Optimal conditions for 5-cyano-2-methylsulfanyl-4(3*H*)-pyrimidinone synthesis is 0.5 M NaOH at 50 ºC, reaction in less alkaline media is favourable for formation of 3-ureidocompounds.
2. Alkylation of 4(3*H*)-pyrimidinones in the presence of potassium carbonate in boiling acetonitrile readily gives a mixture of *O*- N_3-, N_1-alkylated products (yield of separated components by fractional crystallization respectively: 13–57, 0.3–12 and 3–11 %). By ^{1}H NMR spectral data, *O*-alkylated isomer is a major product, N_3- and N_1-alkylated products proportions varied depending on the nature of the substitute on the aromatic ring 4-position and decreasing in order: $CH_3O > CH_3 > H > Br \geq Cl > NO_2$.
3. For N_1-, N_3-, and *O*-alkylated isomers structure estimation are important such spectral characteristics:
   a) In ^{1}H NMR spectrums are typical XCH_2 (X=O, N) and H-6 chemical shifts in a field: 5.99–6.11 and 8.93–8.96 for *O*-alkylated isomers, 5.66–5.82 and 8.63–8.69 for N_3-isomers, 5.69–5.86 and 8.58–8.61 ppm for N_1-isomers respectively.
   b) In ^{13}C NMR spectrums are typical chemical shifts of XCH_2 (X=O, N) and pyrimidine ring C-4 position in a field: 70.0–70.5 and 167.3–167.6 for *O*-alkylated isomers, 51.4–52.2 and 170.6–170.7 for N_3-isomers, 58.9–59.5 and 163.0–163.1 ppm for N_1-isomers respectively.
   c) In IR spectrum are observed valence vibrations absorption bands of CN and CO groups: 2226–2232 and 1686–1705 for *O*-alkylated isomers, 2224–2234,

1690–1698 and 1678–1685 for N_3-isomers, 2226–2229, 1684–1692 and 1652–1623 cm^{-1} for N_1-isomers respectively.

4. New synthesis method for furo[2,3-*d*]pyrimidine system was proposed by cyclization of 4-[4′-*R*-phenacyloxy]-2-methylsulfonylpyrimidin-5-carbonitriles under Thorpe-Ziegler basic conditions. It has been determined that:
   a) The best yields of 5-amino-6-(4′-*R*-benzoyl)-2-methylsulfanylfuro[2,3-*d*]pyrimidines obtained in ethanol at 1.5 equivalent of sodium ethoxide.
   b) Cyclization in system CH_3OH–CH_3ONa (2 equivalents or more) leads to displacement reaction of 2-methylsulfanyl- into methoxygroup as byproduct.
   c) Cyclization in system KOH–H_2O–DMF occurs with side hydrolysis reaction of ether group.
   d) In aprotic solvents (CH_3CN, C_6H_6) furo[2,3-*d*]pyrimidines not formed.
5. Acetylation, hydrazinolysis, hydrolysis and oxidation reactions was occurred for functionalization possibilities of 5-amino-6-(4′-*R*-benzoyl)-2-methylsulfanylfuro[2,3-*d*]pirimidines. 5-Acetylaminoderivatives are formed under acetylation in acetic anhydride. Oxidation reaction occurs with formation of 2-methylsulfonylcompound and Baeyer-Villiger oxidation of ketone group.

LIST OF THE PUBLICATIONS

In the journals included in the list of Institute of Scientific Information (ISI)

1. V. Gefenas, Z. Stankeviciute, and A. Malinauskas. N(1)-, N(3)-,and O-alkylation of 5-cyano-2-methylsulfanyl-4(3H)-pyrimidinone by 4-substituted ω-bromoacetophenones in the system acetonitrile-K_2CO_3. *Chemistry of Heterocyclic Compounds,* 2009, Vol. 45, No. 11, p. 1413–1415.

2. В. Гефенас, Ж. Станкявичюте, А. Малинаускас, С. Тумкявичюс. К вопросу внутримолекулярной циклизации этилового эфира (*E*)-3-(*S*-метилизотиоуреидо)-2-циано-2-пропеновой кислоты. *Химия гетероциклических соединений*, 2010, No. 3, с. 456–460.

3. В. Гефенас, Ж. Станкявичюте, А. Малинаускас. Новый метод синтеза фуро[2,3-*d*]пиримидинов путем циклизации 4-(фенацилокси)пиримидин-5-карбонитрилов. *Химия гетероциклических соединений*, 2010, No. 3, с. 464–467.

Conference materials

1. Stankevičiūtė Ž., Vaitiulionytė D., Gefenas V., Malinauskas A. 5-Cian-2-metilsulfanil-4(3*H*)-pirimidinono O- ir N-alkilinimo ω-bromacetofenonais produktų ciklizacijos reakcijos. // Mokslinės konferencijos ,,Organinė chemija" pranešimų medžiaga. - Kaunas, 2006 m. - Kaunas: Technologija, 2006. p. 66–67. ISBN 9955-25-050-X.

2. R. Voronovič, Ž. Stankevičiūtė, V. Gefenas. 3-(*S*-Alkilizotioureido)-2-cianpropeno rūgščių etilesterių ciklizacijos reakcijos. // Mokslinės konferencijos ,,Organinė chemija", skirtos Organinės chemijos katedros 85-mečiui paminėti, pranešimų medžiaga. – Kaunas, 2007 m. - Kaunas: Technologija, 2007. p. 77–78. ISBN 978-9955-25-246-7.

3. Ž. Stankevičiūtė, B. Abrutytė, V. Gefenas, A. Malinauskas. 2-Alkilsulfanil-4(3*H*)-pirimidinonų ir *ω*-bromacetofenonų sąveikos tyrimas ^{1}H BMR metodu. // Mokslinės konferencijos ,,Organinė chemija", skirtos Organinės chemijos katedros 85-mečiui paminėti pranešimų medžiaga. – Kaunas, 2007 m. - Kaunas: Technologija, 2007. p. 79–80. ISBN 978-9955-25-246-7.

4. V. Gefenas, Ž. Stankevičiūtė, D. Vaitiulionytė, R. Voronovič and A. Malinauskas. Synthesis and Reactions of New Substituted Furo[2,3-*d*]pyrimidines // International Conference on Organic Synthesis BOS 2008 konferencijos pranešimų medžiaga. – Vilnius, 2008 m. - Vilnius: Vilniaus universitetas, 2008. p. 80. ISBN 978-9955-33-265-7.

5. Gefenas, Ž. Stankevičiūtė, A. Malinauskas. Oxidacion of 5-amino-2-methylsulfanyl-6-phenacylfuro[2,3-*d*]pyrimidines with peroxycarboxylic acids. // 9-osios Lietuvos chemikų konferencijos ,,Chemija 2009", skirtos akademiko Juozo Matulio 110 metų gimimo sukakčiai pranešimų medžiaga. – Vilnius, 2009 m. spalio 16 d. ISBN 978-9986-702-17-7.

ALKILINTŲ 5-CIAN-2-METILSULFANIL-4(3*H*)-PIRIMIDINONŲ SINTEZĖS IR CIKLIZACIJOS REAKCIJŲ TYRIMAS

REZIUMĖ

Ciklizuojant pradinį (*E*)-2-cian-3-(*S*-metilizotioureido)-2-propeno rūgšties etilesterį ledinėje acto rūgštyje selektyviai susidaro 4-amino-2-metilsulfanilpirimidin-5-karboksirūgšties etilesteris, o šarminėmis katalizės sąlygomis be ciklizacijos produktų – 5-cian-2-metilsulfanil-4(3*H*)-pirimidinono ir 4-amino-2-metilsulfanil-5-pirimidin-5-karboksirūgšties etilesterio, pirmą kartą, kaip individualūs junginiai, išskirti hidrolizės produktai – (*E*)- ir (*Z*)-2-cian-3-ureido-2-propeno rūgščių etilesteriai. Ištirta tridentatinio 5-cian-2-metilsulfanil-4(3*H*)-pirimidinono sąveika su 4-padėtyje pakeistais *ω*-bromacetofenonais: alkilinant sistemoje $CH_3CN–K_2CO_3–[KI]$ išskirtos ir identifikuotos visos trys izomerų serijos – 4-(4′-*R*-fenaciloksi)-2-metilsulfanil-5-pirimidinkarbonitrilai (pagrindinis reakcijos *O*-alkilproduktas) ir minoriniai N_1- ir N_3-alkilinimo produktai. ^{1}H BMR metodu nustatyta, kad mišiniuose vyrauja *O*-alkilizomeras, o N_1- ir N_3-alkilizomerų santykis priklauso nuo pakaito benzeno žiedo 4-oje padėtyje prigimties. Pasiūlytas naujas furo[2,3-*d*]pirimidino heterociklinės sistemos sintezės būdas 4-(4′-*R*-fenaciloksi)-2-metilsulfanil-5-pirimidinkarbonitrilų ciklizacija Torpo-Ciglerio bazinėmis sąlygomis ir ištirtos susintetintų 5-amino-6-(4′-*R*-benzoil)-2-metilsulfanilfuro[2,3-*d*]pirimidinų acetilinimo, oksidavimo, hidrolizės bei hidrazinolizės reakcijos.

Information about the autor

Name, Surname	Živilė Stankevičiūtė
Birth date and place	1977 09 20, Varėna

Education

1983–1995	„A. Ryliškis“ secondary school, Senoji Varėna
1995–1999	Vilnius Pedagogical University, bachelor degree in chemistry and teacher qualification
1999–2001	Vilnius Pedagogical University, master degree in chemistry and teacher qualification
2004–2009	Doctoral studies at the Institute of Chemistry

Work experience

2001/02–2006/09	Vilnius Pedagogical University, Faculty of Natural Sciences, Department of Chemistry, laboratory technician
From 2006/10	Vilnius Pedagogical University, Faculty of Natural Sciences, Department of Chemistry, assistant

Informacija apie autorių

Vardas, Pavardė	Živilė Stankevičiūtė
Gimimo vieta ir data	1977 09 20, Varėna

Išsilavinimas

1983–1995	A. Ryliškio vidurinė mokykla, Senoji Varėna
1995–1999	Vilniaus Pedagoginis universitetas, bakalauro laipsnis ir chemijos mokytojo kvalifikacija
1999–2001	Vilniaus Pedagoginis universitetas, magistro laipsnis ir chemijos mokytojo kvalifikacija
2004–2009	Doktorantūros studijos Chemijos institute

Darbo patirtis

2001/02–2006/09	Vilniaus Pedagoginis universitetas, gamtos mokslų fakultetas, chemijos katedra, laborantė
Nuo 2006/10	Vilniaus Pedagoginis universitetas, gamtos mokslų fakultetas, chemijos katedra, asistentė