VILNIUS UNIVERSITY

CPST INSTITUTE OF CHEMISTRY

ROBERTAS JUŠKĖNAS

SYNTHESIS OF TRICYCLIC HETEROSYSTEMS BASED ON PYRAZOLO[3,4-*d*]PYRIMIDINE FRAMEWORK. STUDY OF INTRAMOLECULAR REACTION OF PYRIMIDINE NITROGEN WITH *O,O*-ACETALS

SUMMARY OF DOCTORAL DISSERTATION

Physical sciences, chemistry (03P)

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The thesis defense will take place on June 27, 2014, at 12 h. at the Auditorium of Inorganic Chemistry at the Faculty of Chemistry of Vilnius University.

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VILNIAUS UNIVERSITETAS
FMTC CHEMIJOS INSTITUTAS

ROBERTAS JUŠKĖNAS

TRICIKLIŲ HETEROSISTEMŲ, TURINČIŲ PIRAZOLO[3,4-*d*]PIRIMIDINO FRAGMENTĄ, SINTEZĖ. INTRAMOLEKULINĖS PIRIMIDINO AZOTO ATOMO REAKCIJOS SU *O,O*-ACETALIAIS TYRIMAS

Daktaro disertacijos santrauka
Fiziniai mokslai, chemija (03P)

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Contents

Introduction

Since the dawn of heterocyclic chemistry the developments in this field of chemistry had a great influence on evolution of science and industry. The products of this branch of chemistry have found a wide range of applications in numerous areas – pharmaceutics, agricultural chemistry, industry of dyes, photography and photophysics. The knowledge of heterocyclic chemistry has allowed to understand crucial biological processes, including one of the most important questions in life science – storage and replication of genetic information. Heterocyclic compounds are also used as ligands in transition-metal catalysis, or as organic catalysts, thus helping to solve synthetic chemistry problems.

The main task of heterocyclic chemistry is the search for the new, more effective synthetic methods for obtaining heterocyclic derivatives. That covers not only the formation of heterocycles, but also their functionalization, which leads to creation of compounds having various chemical and physical properties. The development of new synthetic methods is not only important for heterocyclic chemistry itself but it also promotes the progress of other research areas. For example, Huisgen cycloaddition reaction has found its application in the fields of biochemistry, pharmacochemistry and polymer and supramolecular chemistry. The development of heterocycle-based ionic liquids has expanded the limits of their physical properties as well as application capabilities. The progress of heterocyclic chemistry is important for various scientific areas and for the industry.

Pyrazolo[3,4-*d*]pyrimidine as 7-deaza-8-azapurine analogue is very important pharmacologically. In living organisms, the derivatives of this heterocycle may interfere in the biochemical processes of purine metabolism and interact with enzymes recognizing the purine moiety. Allopurinol, a simple derivative of pyrazolo[3,4-*d*]pyrimidine, is the inhibitor of xanthine oxidase and for more than 50 years is used for the treatment of conditions associated with an excess of uric acid. However, the greater potential for this heterocycle lies in its interaction with kinases. These enzymes use ATP as substrate and take part in regulation of cell enzymes. Therefore, selective regulation of kinases may help to cure various diseases. Src kinase and cyclin-dependent kinase inhibitors are potential anticancer agents. The regulation of glycogen synthase kinase-3 may be the way to fight

against type-2 diabetes, while the inhibition of mitogen activated protein kinase p38 may be useful in treating autoimmune diseases. Pyrazolo[3,4-*d*]pyrimidine derivatives are found amongst inhibitors of these enzymes. Polycyclic heterosystems containing pyrazolo[3,4-*d*]pyrimidine framework are also in interest. Compounds exhibiting anticancer, antibacterial, fungicidal, antiviral properties are amongst these polycyclic derivatives. Pyrazolo[3,4-*d*]pyrimidines fused with triazole ring are selective adenosine receptors antagonists and are used in studies of neurochemical processes. Commercially available compounds SCH 58261 and SCH 442416 are A_{2A}, and MRE 3008-F20 - A_3 receptors antagonists. A selective A_1 receptor antagonist with this heterocyclic framework has also been created recently. In addition, polycyclic heterosystems based on pyrazolo[3,4-*d*]pyrimidine exhibit properties of bioactivity that are not related with biochemical processes of purine derivatives. These properties are phosphodiesterase (PDE1) inhibition and anti-inflammatory activity. Thus, the search for new types of heterocyclization reactions and development of new functionalization methods is an important task of organic chemistry, whereas the fused heterocycles based on pyrazolo[3,4-*d*]pyrimidine framework is interesting and promising research object.

The main goals of the present work were:

- The development of new synthetic methods for the synthesis of tricyclic *peri*-fused heterosystems based on pyrazolo[3,4-*d*]pyrimidine scaffold;
- The development of the synthesis method of compounds with 3-ethoxy-2,3-dihydroimidazo[1,2-*c*]pyrimidine moiety and the evaluation of the potential for the modification of these compounds.

The tasks for the achievement of the aims:

1. To synthesize new *orto*- and *peri*-fused heterocyclic systems from 3-amino-4-chloropyrazolo[3,4-*d*]pyrimidine derivative.
2. To find suitable conditions for the cyclization of 4-(2,2-diethoxyethyl)aminopyrimidines to 2,3-dihydroimidazo[1,2-*c*]pyrimidines. Investigate the influence of functional groups in pyrimidine moiety on the course of this reaction.
3. To investigate the scope of replacement of ethoxy group with nucleophiles in 3-ethoxy-3,7-dihydro-2*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidines and the interaction of these compounds with oxidative agents.

Scientific novelty:

Three new *orto*- and *peri*-fused heterocyclic systems based on pyrazolo[3,4-*d*]pyrimidine scaffold were synthesized. The suitable conditions for the cyclization of 4-(2,2-diethoxyethyl)aminopyrimidines to 2,3-dihydroimidazo[1,2-*c*]pyrimidines were found. The influence of functional groups in pyrimidine moiety for the course of this reaction was investigated. It has been shown that functional groups including alkylthio, cyano, amino, formyl are tolerated in this type of reaction. The method for the replacement of ethoxy group with benzylthio group in 3-ethoxy-2,3-dihydroimidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidines has been found. It has been shown that the opening or destruction of imidazole ring take place when 3-ethoxy-2,3-dihydroimidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidines are oxidized under conditions for oxidation of acetals.

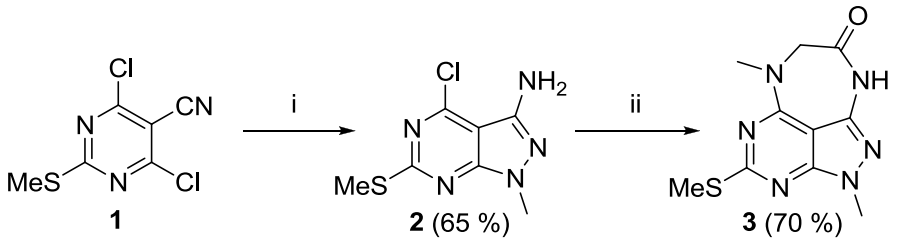
Main statements for the defence:

1. 1,2,3,5,6,9-Hexaazabenz[*cd*]azulene, 6-thia-1,2,3,5,9-pentaazabenz[*cd*]azulene and 1,2,3,5,6,7,9-heptaazabenz[*cd*]azulene heterocyclic systems can be synthesized by treatment of the 3-amino-4-chloro-1-methyl-6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidine with compounds possessing nucleophilic and electrophilic centers.
2. 4-(2,2-Diethoxyethyl)aminopyrimidines undergo cyclization to 2,3-dihydroimidazo[1,2-*c*]pyrimidines under acidic conditions.
3. The substitution of nucleofuges with hydroxyl groups in pyrimidine ring takes place when imidazo[1,2-*c*]pyrimidinium salts without labile hydrogen atom are treated with sodium hydroxide solution.
4. 3-Ethoxy-7-methyl-5-methylthio-2,7-dihydro-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine participates in the substitution reaction of ethoxy group with benzylthio group.

Results and discussion

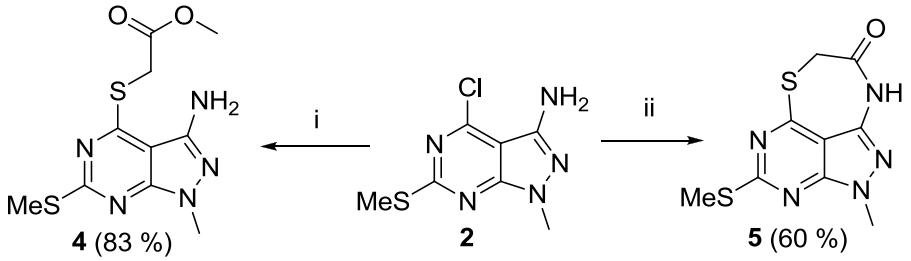
Synthesis of *orto*- and *peri*-fused heterosystems based on pyrazolo[3,4-*d*]pyrimidine framework

For the synthesis, an easily available 3-amino-4-chloro-1-methyl-6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidine (**2**) has been used as a starting material. This compound was synthesized from pyrimidine **1** by a modified procedure according to the one reported earlier. The treatment of pyrazolo[3,4-*d*]pyrimidine **2** with methyl *N*-methylaminoethanoate in the presence of potassium carbonate gave 1,2,3,6,7,9-heksaazabenz[*cd*]azulene **3**.



Scheme 1.

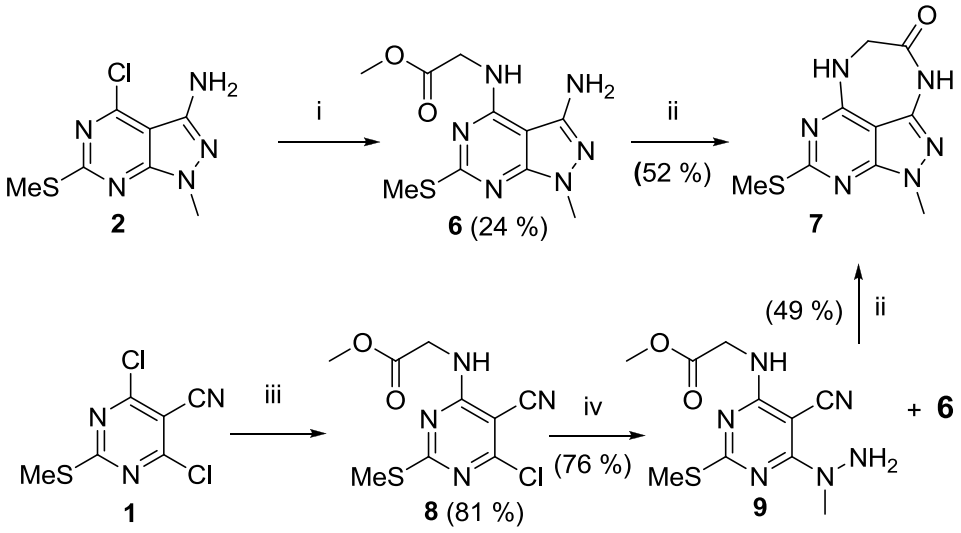
Only nucleophilic substitution of chlorine atom took place when pyrazolo[3,4-*d*]pyrimidine **2** was treated with methyl mercaptoethanoate under the same reaction conditions. 6-Thia-1,2,3,5,9-pentaazabenz[*cd*]azulene **5** was synthesized using more rigorous conditions (100 ºC in DMF).



Scheme 2.

In order to expand this method for the synthesis of similar *ortho*- and *peri*-fused heterocycles, compound **2** was treated with methyl aminoethanoate. However, under the conditions described for the synthesis of **3**, only starting materials were recovered. Performing the reaction at 100 ºC in DMF in the presence of potassium carbonate gave the substitution reaction product **6**. It was found that 1,2,3,6,7,9-heksaazabenz[*cd*]azulene **7**

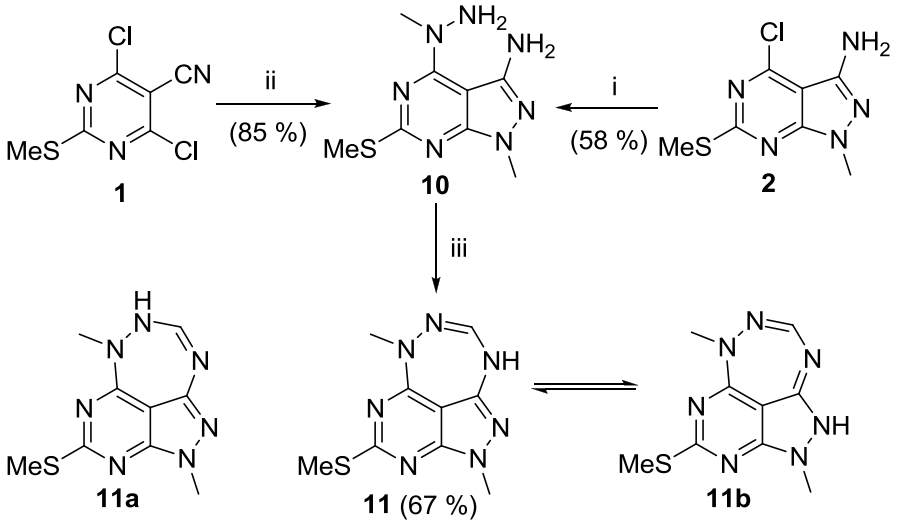
can be formed when compound **6** is heated in acetic acid. The total yield of these two reactions was only 12 %, therefore an alternative way for the synthesis of the compound **7** was applied. Compound **8** was synthesized by the reaction of pyrimidine **1** with methyl aminoethanoate in the presence of sodium carbonate. A mixture of compounds **6** and **9** was formed when pyrimidine **8** was treated with methylhidrazine. This mixture was cyclized to *peri*-fused system **7** by heating it in acetic acid.



i: $NH_2CH_2CO_2Me{\cdot}HCl$, K_2CO_3, DMF, 90-100 ºC, 1 h;
ii: AcOH, 90 ºC, 1 h;
iii: $NH_2CH_2CO_2Me{\cdot}HCl$, Na_2CO_3, MeOH, rt, 30 min;
iv: $MeNHNH_2$, MeOH, rt, 75 min.

Scheme 3.

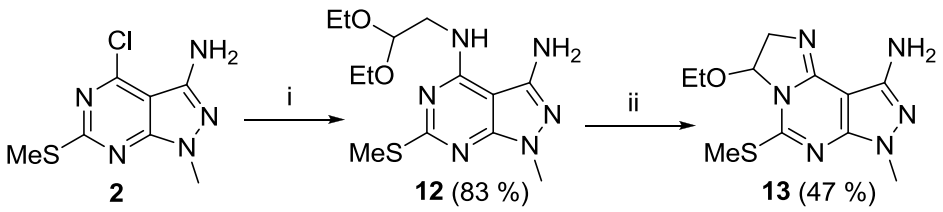
1,2,3,5,6,7,9-Heptaazabenz[*cd*]azulene heterocyclic system was synthesized by two step reaction sequence from pyrazolo[3,4-*d*]pyrimidine **2**. The substitution of chlorine atom yielded the compound **10**, which was also synthesized by treating pyrimidine **1** with an excess of methylhidrazine. The formation of *peri*-fused heterosystem **11** was completed by performing cyclization with triethoxymethane. The formation of two compounds – **11** and **11a** is possible in this reaction. NOESY experiment could help to determine which of the structures was formed, however this experiment could not be performed due to overlap of N^6CH_3 group and residual water signals. The formation of structure **11** was confirmed from indirect evidence – equilibrium with **11b** in low-polar solvents, and from the analogy of formation of similar heterocyclic system reported earlier.



i: $MeNHNH_2$, THF, rt, 1.5 h;
ii: $MeNHNH_2$, THF, rt, 30 min;
iii: $HC(OEt)_3$, dioxane, NH_4Cl, Δ, 13 h.

Scheme 4.

Ortho- but not *peri*-fused heterocyclic system was obtained when acetal group was chosen as electrophilic partner for reaction with the amino group of pyrazolo[3,4-*d*]pyrimidine **2**. Acetal fragment was introduced into pirazolo[3,4-*d*]pyrimidine **2** by treating it with 2,2-diethoxyethylamine. The resulted compound **12** formed imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine **13** upon treatment with acetic acid.



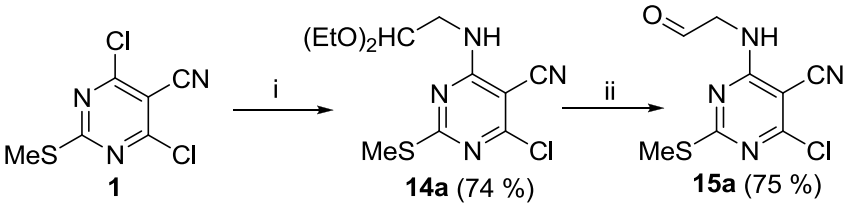
i: $NH_2CH_2CH(OEt)_2$, NEt_3, *i*-PrOH, Δ, 3 h;
ii: AcOH, 100 °C, 30 min.

Scheme 5.

Reactions, when pyridine type nitrogen atom attacks an acetal fragment, are not unknown, but only few examples of this type of reaction can be found in literature. Also literature review revealed that this reaction has a potential to be applied for the synthesis of functionalized dihidroimidazo[1,2-*c*]pyrimidines.

Study of intramolecular reaction of pyrimidine nitrogen with *O,O*-acetals

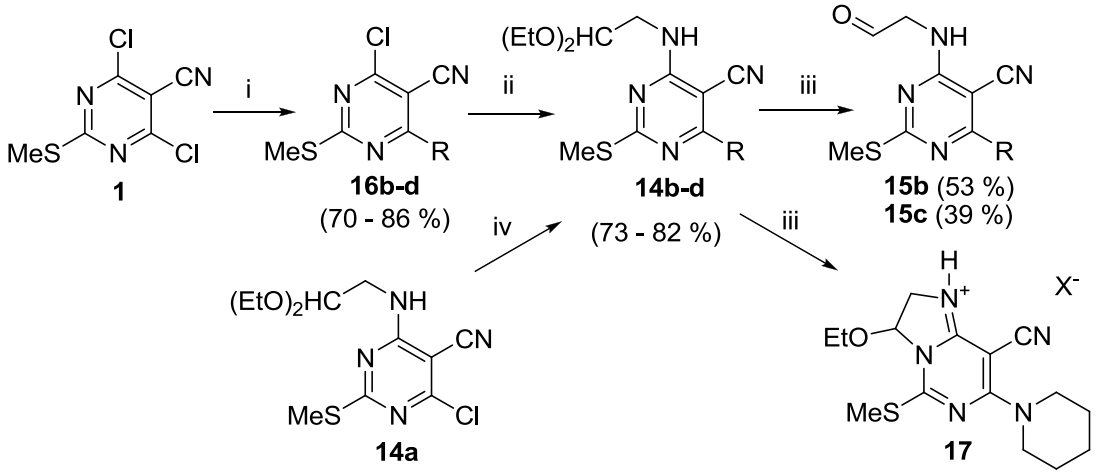
Pyrimidine **1**, as easy accessible and functionizable heterocycle, was chosen for further investigation of formation of dihidroimidazo[1,2-*c*]pyrimidine by the reaction between pyrimidine nitrogen and acetal fragment. Acetal group was introduced into pyrimidine **1** by nucleophilic substitution of chlorine atom. The obtained compound **14a** formed aldehyde **15a** upon treatment with acetic acid.



i: $NH_2CH_2CH(OEt)_2$, Na_2CO_3, MeOH, rt, 1 h;
ii: AcOH, rt, 8 days.

Scheme 6.

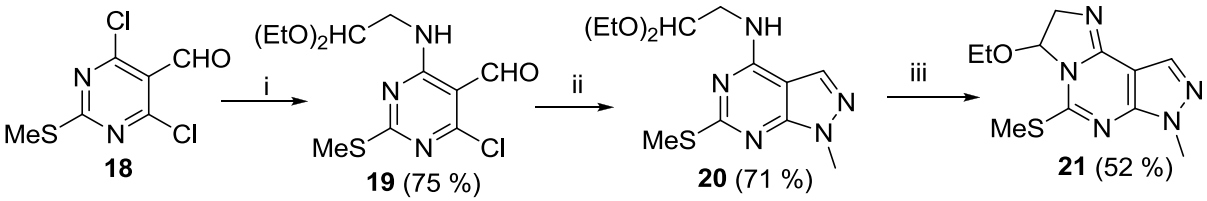
To enhance the electron density and nucleophilicity of pyrimidine nitrogen, compounds **14b-d** were synthesized by two step reaction sequence. Compounds **14b**,**c** failed to give target dihydroimidazo[1,2-*c*]pyrimidines upon treatment with acetic acid and formed aldehydes **15b,c** instead. While compound **14d** yielded 2,3-dihydroimidazo[1,2-*c*]pyrimidinium derivative **17**. The anion of this compound was never determined.



R = OMe (**b**):
i: MeOH, NEt_3, rt, 2 h; ii: $NH_2CH_2CH(OEt)_2$, NEt_3, MeOH, rt, 20 h; iii: AcOH, rt, 20 days.
R = NMe_2 (**c**):
i: $HNMe_2$, MeOH, rt, 5 min.; ii: $NH_2CH_2CH(OEt)_2$, NEt_3, *i*-PrOH, Δ, 6 h;
iii: AcOH, rt, 8 days; iv: Me_2NH, *i*-PrOH, rt, 1,5 h.
R = $(CH_2)_5N$ (**d**):
i: $(CH_2)_5NH$, MeOH, rt, 5 min; ii: $NH_2CH_2CH(OEt)_2$, NEt_3, *i*-PrOH, Δ, 6 h;
iii: AcOH, rt, 8 days.

Scheme 7.

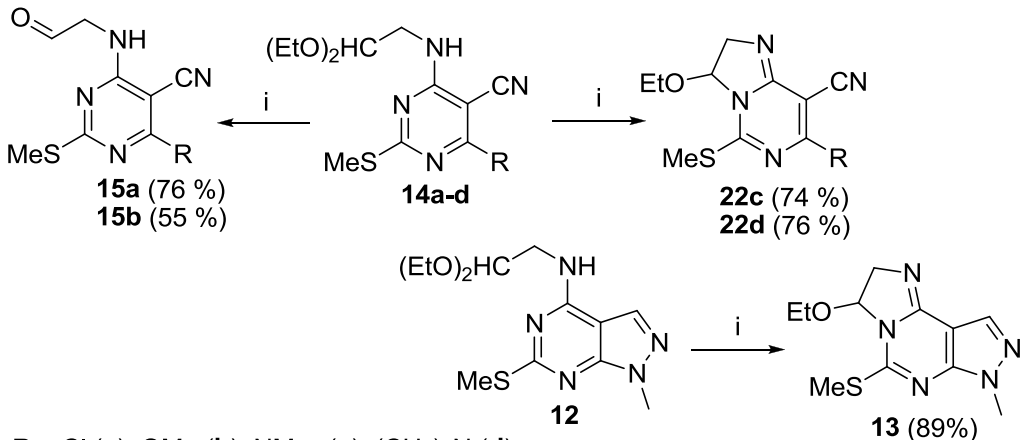
The formation of compound **17** proved that 4-(2,2-diethoxyethylamino)pyrimidines can undergo cyclization to 2,3-dihydroimidazo[1,2-*c*]pirimidines. In order to find more suitable conditions for this reaction pyrazolo[3,4-*d*]pyrimidine **20** was synthesized from pyrimidine **18** as a model compound for investigation. Various acidic conditions were investigated for the cyclization of compound **20** to imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine **21**. Best results were achieved when reaction was performed using boron trifluoride as acidic component. For the neutralization of the product sodium carbonate solution was used.



i: $NH_2CH_2CH(OEt)_2$, NEt_3, *i*-PrOH, rt, 10 min;
ii: $MeNHNH_2$, *i*-PrOH, rt, 30 min;
iii: $BF_3 \cdot Et_2O$, CH_2Cl_2, rt, 2 h.

Scheme 8.

These conditions were then applied for the cyclization of compounds **14a-d** and **12**. Pyrimidines **14a**,**b** formed aldehydes, while compunds **14c**,**d** and **12** underwent cyclization to imidazo[1,2-*c*]pyrimidines **22c**,**d** and **13**.

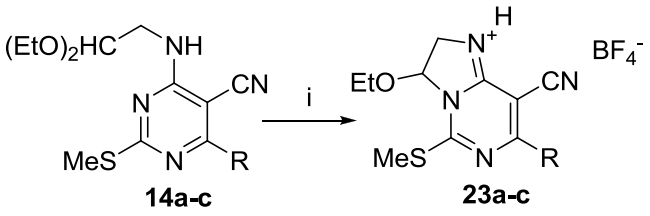


R = Cl (**a**), OMe (**b**), NMe_2 (**c**), $(CH_2)_5N$ (**d**).
i: 1. $BF_3 \cdot Et_2O$, CH_2Cl_2, rt; 2. Na_2CO_3 (aq.)

Scheme 9.

To find out whether aldehydes **15a**,**b** were formed during the isolation procedure or a cyclization involving pyrimidine nitrogen atom did not take place at all, attempts to isolate the reaction intermediates – 2,3-dihydroimidazo[1,2-*c*]pyrimidinium salts – were made. Pyrimidines **14a-c** were treated with boron trifluoride, and after the cyclization took place (TLC control) the solvent was removed and salts **23a-c** were precipitated with

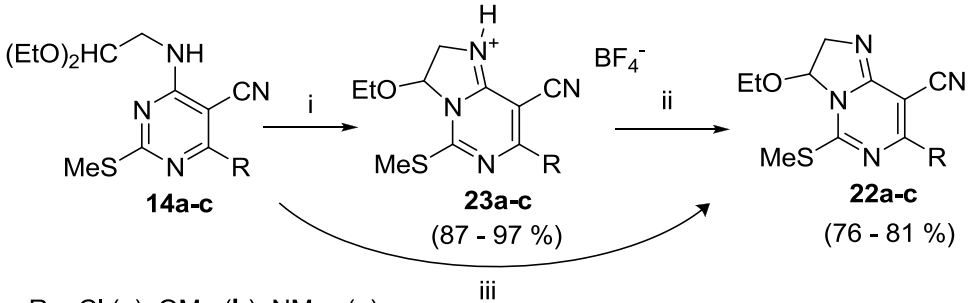
diethylether. ^{19}F NMR spectra revealed that the counterion of these salts is tetrafluoroborate.



R = Cl (**a**), OMe (**b**), NMe_2 (**c**);
i: $BF_3 \cdot Et_2O$, CH_2Cl_2, rt.

Scheme 10.

The attempts to deprotonate imidazo[1,2-*c*]pyrimidinium salt **23c** in non-nucleophilic media were made. Strong bases such as potassium phosphate and DBU appeared to be suitable for this purpose. However, pure compounds could not be obtained using this isolation procedure. The trituration of solutions of these compounds with water and chromatographic separation appeared to be an essential procedures for isolating pure substances. Since the work-up of the reaction mixtures with aqueous sodium bicarbonate gave aldehydes in some cases, sodium hydroxide solution was employed for the deprotonation of 2,3-dihydroimidazo[1,2-*c*]pyrimidinium salts in the reaction work-up phase. This procedure led to the isolation of the target 2,3-dihydroimidazo[1,2-c]pyrimidines **22a-c** in good yields. Hence, the basicity of the work-up solution seems to be the key factor determining the reaction course.



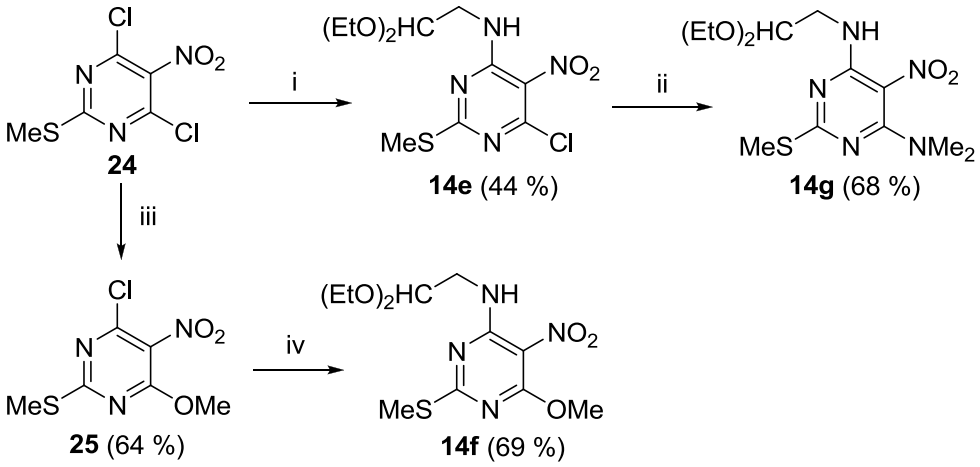
R = Cl (**a**), OMe (**b**), NMe_2 (**c**).
i: $BF_3 \cdot Et_2O$, CH_2Cl_2, rt;
ii: NaOH (aq);
iii: 1.$BF_3 \cdot Et_2O$, CH_2Cl_2, rt; 2. NaOH (aq).

Scheme 11.

To explore the scope of this reaction the series of 4-(2,2-diethoxyethyl)aminopyrimidines **14e-j** were synthesized. Nitro-group-containing pyrimidines **14e-g** were chosen for several reasons. As an electron-withdrawing substituent nitro group should reduce the reactivity of the pyrimidine nitrogen atom. Also,

intermediate salts were expected to be less stable. On the other hand, target 2,3-dihydroimidazo[1,2-*c*]pyrimidines, as *N*,*O*-acetals, should be stable, as it is known that electron acceptors on the nitrogen atom stabilize *N*,*O*-acetals.

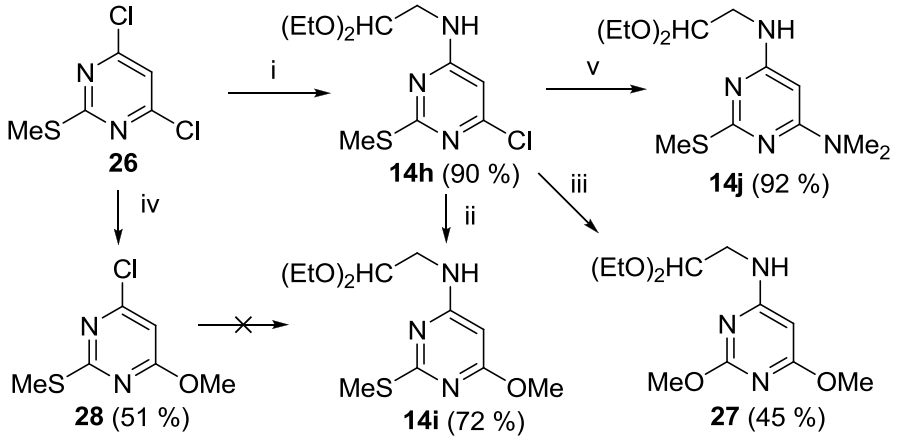
4-(2,2-diethoxyethyl)amino-5-nitropyrimidines **14e-g** were synthesized from pyrimidine **24** by the substitution of chlorine atoms. The introduction of 2,2-diethoxyethylamino group proceeded only in moderate yield. The introduction of methoxy group into compound **14e** failed, thus another synthetic pathway was chosen for the synthesis of pyrimidine **14f**. Firstly, methoxy group was introduced into compound **24** and subsequent substitution of chlorine with 2,2-diethoxyethylamine moiety was performed. A dimethylamino group containing compound **14g** was synthesized from pyrimidine **14e**.



i: $NH_2CH_2CH(OEt)_2$, Na_2CO_3, *i*-PrOH, rt, 5 min;
ii: Me_2NH, *i*-PrOH, rt, 15 min;
iii: MeOH, Na_2CO_3, rt, 5 h;
iv: $NH_2CH_2CH(OEt)_2$, NEt_3, *i*-PrOH, rt, 45 min.

Scheme 12.

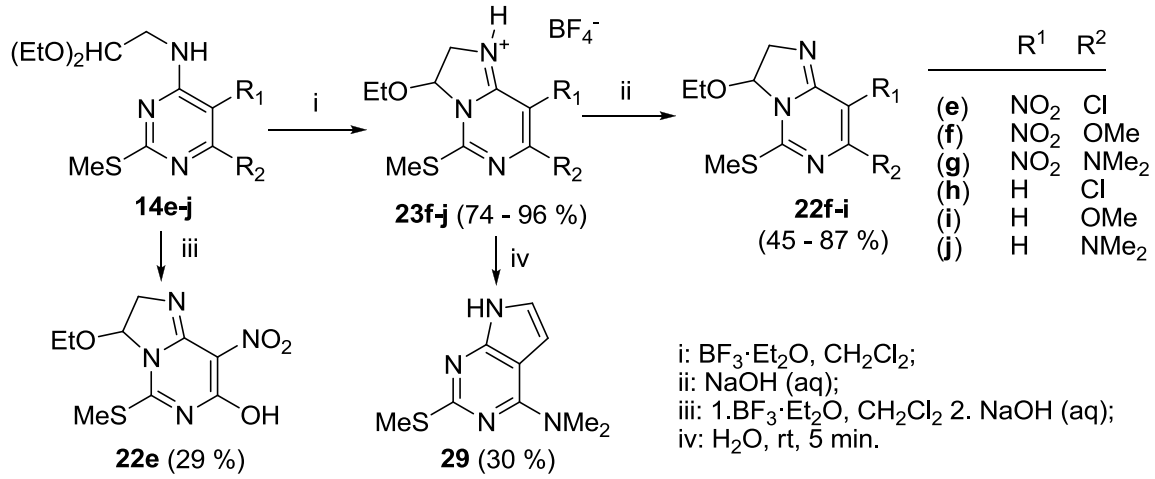
For the synthesis of 5-unsubstituted pyrimidines **14h-j** compound **26** was chosen as starting material. The introduction of 2,2-diethoxyethylamino fragment into the 4-position of pyrimidine went smoothly. Subsequent substitution of chlorine atom with dimethylamine also proceeded well. However, introduction of methoxy group into compound **14h** did not take place under mild reaction conditions, and disubstitution product **27** was formed when methoxide in polar aprotic solvents was applied. Another pathway to obtain pyrimidine **14i** was useless as 2,2-diethoxyethylamino group could not be introduced into compound **28**. The formation of target pyrimidine **14i** was achieved by heating compound **14h** at 100 °C in methanol in the presence of sodium methoxide in a closed reaction vessel.



i: $NH_2CH_2CH(OEt)_2$, NEt_3, *i*-PrOH, 65 °C, 3 h; ii: NaOMe, MeOH, 100 °C, 16 h;
iii: NaOMe, *N*-methylpyrrolidone, 110 °C, 12 h; iv: MeOH, NEt_3, 120 °C, 5 h;
v: Me_2NH, dioxane, 100 °C, 6 h.

Scheme 13.

The treatment of pyrimidines **14f-j** with boron trifluoride gave the corresponding 2,3-dihydroimidazo[1,2-*c*]pyrimidinium salts **23f-j** in good to excellent yields. Attempts to isolate 7-chloro-3-ethoxy-5-methylthio-8-nitro-2,3-dihydroimidazo[1,2-*c*]pyrimidin-1-ium salt, formed in the reaction of **14e** with boron trifluoride, resulted in obtaining complex mixture of compounds. Nevertheless, work-up with aqueous NaOH without isolation of the salt gave 7-hydroxy-2,3-dihydroimidazo[1,2-*c*]pyrimidine **22e** in low yield. The target compounds **22f-i** can be obtained either from isolated 2,3-dihydroimidazo[1,2-*c*]pyrimidinium salts **23f-i** or directly from pyrimidines **14f-i**. However, all attempts to isolate 3-ethoxy-7-dimethylamino-5-methylthio-2,3-dihydroimidazo[1,2-*c*]pyrimidine by normal- or reverse-phase chromatography or by crystallization failed. Pyrrolo[2,3-*d*]pyrimidine **29** was formed when imidazo[1,2-*c*]pyrimidinium salt **23j** was treated with water.

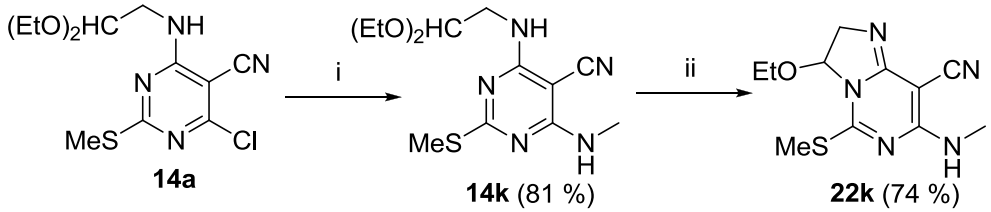


i: $BF_3{\cdot}Et_2O$, CH_2Cl_2;
ii: NaOH (aq);
iii: 1.$BF_3{\cdot}Et_2O$, CH_2Cl_2 2. NaOH (aq);
iv: H_2O, rt, 5 min.

Scheme 14.

The nature of the substituent at the 6-position of the pyrimidine has a marked effect on the reaction time. Compounds containing a chlorine group reacted in several minutes, whereas full conversion of pyrimidines bearing a dimethylamino group required two hours. These results were opposite to those expected. It appears, that the pyrimidine nitrogen atom in the dimethylamino derivatives is not only more nucleophilic, but also more basic, thus, its interaction with boron trifluoride slows down the reaction. On the other hand, substituents at the 5-position of pyrimidine have no significant effect on reaction time; however lower yields of 2,3-dihydroimidazo[1,2-*c*]pyrimidines **22h-i** were obtained from 5-unsubstituted pyrimidines **14h**,**i**.

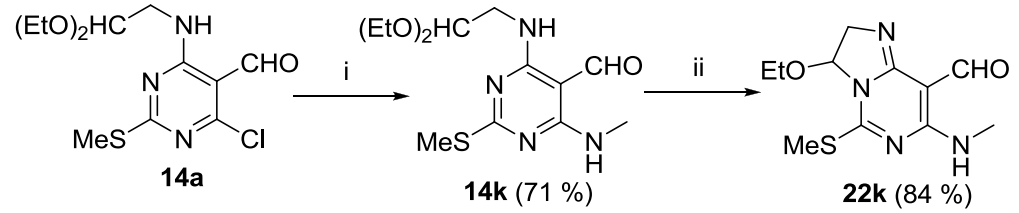
Imidazo[1,2-*c*]pyrimidinium salts **23a-c**,**f-j** contain only one labile hydrogen atom, and only one product can be obtained by deprotonation of these compounds. The possibility to form two products appears when substituents that may also be deprotonated are introduced into the 2- or 6-position of pyrimidine. To define the reaction course in this case the pyrimidine **14k** was synthesized and cyclized with boron trifluoride. Deprotonation proceeded unambiguously and only product **22k** was formed.



i: $MeNH_2$, i-PrOH, rt, 1 h;
ii: 1. $BF_3 \cdot Et_2O$, CH_2Cl_2, rt, 30 min; 2. Na_2CO_3 (aq).

Scheme 15.

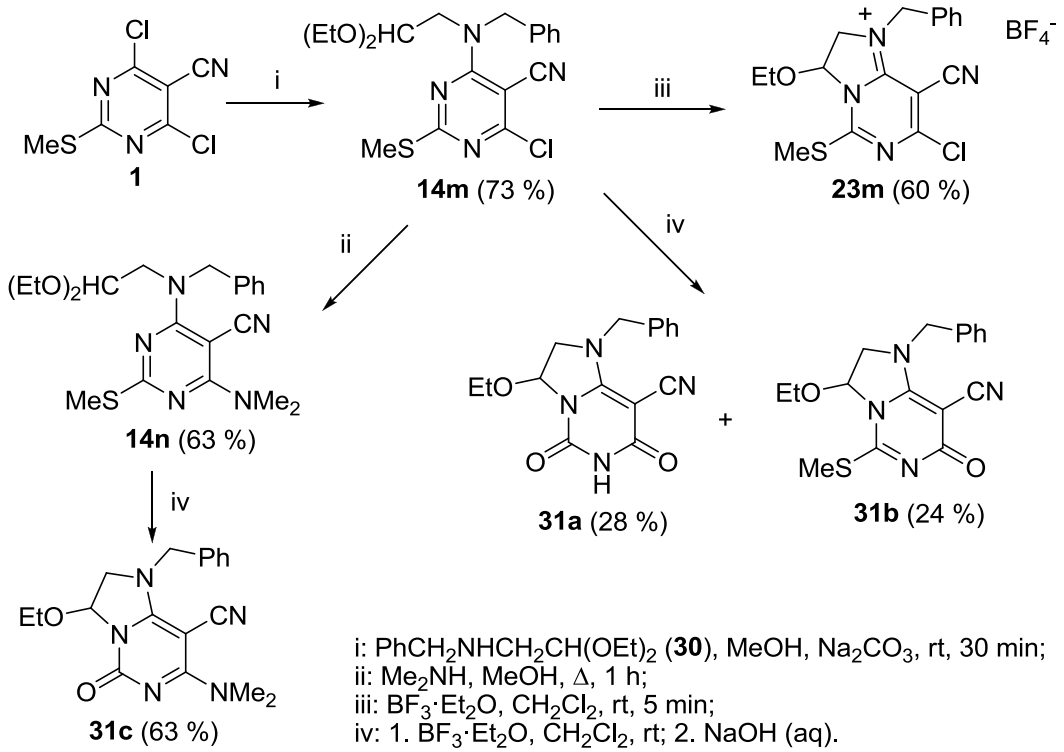
The cyclization reaction of 4-(2,2-diethoxyethyl)aminopyrimidines to 2,3-dihydroimidazo[1,2-*c*]pyrimidines is tolerant to such functional groups as nitro, alkylthio, cyano, amino. However, a formyl group may be intolerant for the conditions of this reaction. To check if this reaction can be applied to substrates containing a formyl group, pyrimidine **14l** was synthesized and cyclized with boron trifluoride. Excellent yield of the imidazo[1,2-*c*]pyrimidine **22l** proved that this reaction is tolerant to formyl group.



i: $MeNH_2$, *i*-PrOH, rt, 1 h;
ii: 1. $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 30 min; 2. Na_2CO_3 (aq).

Scheme 16.

For the formation of neutral imidazo[1,2-*c*]pyrimidines **22** labile hydrogen atom is mandatory. If there is no such atom, other reactions should take place when intermediate salts are treated with aqueous bases. The most plausible one would be opening of imidazole ring with the formation of hemiacetal or aldehyde. However, when pyrimidine **14m** was treated with boron trifluoride and sodium hydroxide solution afterwards, two products identified as imidazo[1,2-*c*]pyrimidines **31a** and **31b** were formed. Hydroxide anion attacked pyrimidine ring instead of the imidazole ring, and nucleophilic substitution products were formed. When the same conditions were applied to pyrimidine **14n** only compound **31c** was formed as dimethylamino group is a poor leaving group.

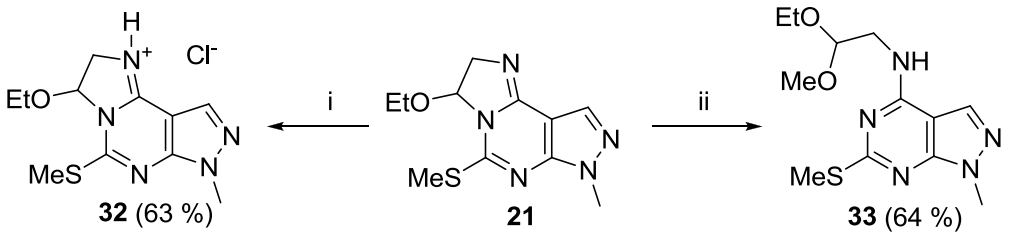


i: $PhCH_2NHCH_2CH(OEt)_2$ (**30**), MeOH, Na_2CO_3, rt, 30 min;
ii: Me_2NH, MeOH, Δ, 1 h;
iii: $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 5 min;
iv: 1. $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt; 2. NaOH (aq).

Scheme 17.

N,*O*-acetal fragment is formed when 4-(2,2-diehoxyethyl)aminopyrimidines undergo cyclization to 2,3-dihydroimidazo[1,2-*c*]pyrimidines. This structural fragment may be exploited for further modification of obtained compounds. Attempts to replace

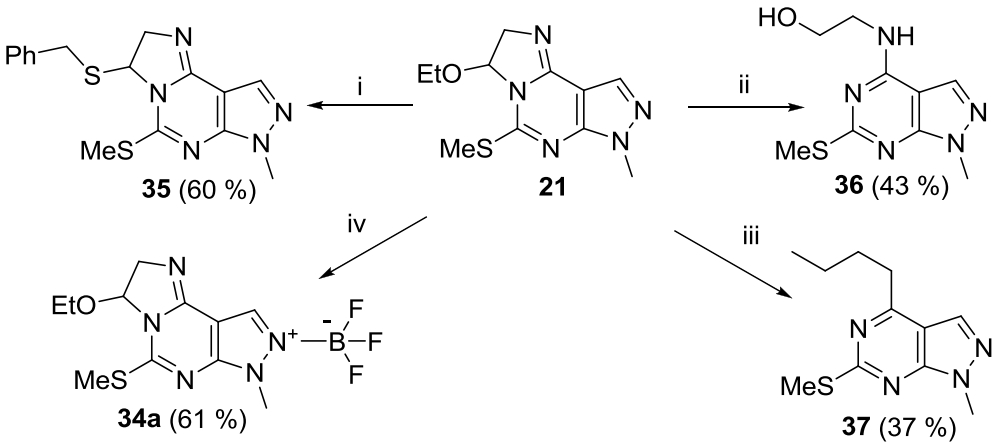
ethoxy group under acidic conditions were made. First of all, the interaction of imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine **21** with protic acid – hydrogen chloride was tested. The nitrogen atom of the imidazole ring was protonated and the salt **32** was formed. Since this nitrogen atom is protonated the attempts to achieve nucleophilic substitution with the use of protic acids would result in imidazole ring opening. That was confirmed when compound **21** was heated in methanol in the presence of hydrochloric acid – mixed acetal **33** was formed.



i: 10 % HCl, $(CH_3)_2CO$, rt, 5 min;
ii: 10 % HCl, MeOH, Δ, 30 min.

Scheme 18.

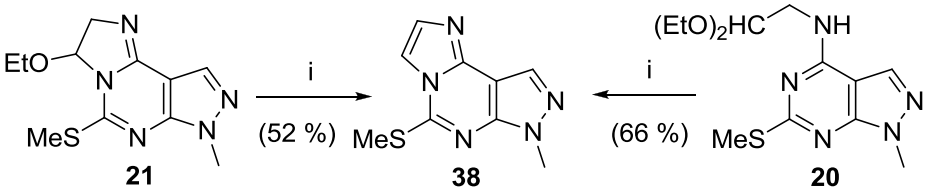
Attempts to apply Lewis acids for the catalysis of substitution of ethoxy group were made. When imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine **21** was treated with benzyl mercaptan in the presence of boron trifluoride only compound **34a** was formed. This compound was also formed when the reaction was performed without benzyl mercaptan. Attempts to use silicon derivatives – trimethylsilylchloride and trimethylsilyltriflate as C-O bond activating agents were unsuccessful – no reaction took place. The substitution of ethoxy group in imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine **21** with benzyl mercaptan was achieved when titanium tetrachloride was used as acidic agent – compound **35** was formed. However, the substitution of ethoxy group did not take place in these conditions when other nucleophiles – benzyl amine, iodide, phenyl magnesium bromide were used. The use of sodium boron hydride resulted in opening of imidazole ring and reduction – pyrazolo[3,4-*d*]pyrimidine **36** was formed. The application of described in literature reaction conditions suitable for the substitution of alkoxy group in *O,O*-acetals using organolithium compounds resulted in formation of 4-butylpyrazolo[3,4-*d*]pyrimidine **37**.



i: $PhCH_2SH$, $TiCl_4$, $Cl(CH_2)_2Cl$, Δ, 20 h;
ii: $NaBH_4$, $TiCl_4$, $Cl(CH_2)_2Cl$, Δ, 12 h;
iii: $BF_3{\cdot}Et_2O$, *n*-BuLi, THF, -80 °C, 30 min;
iv: $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 1 h.

Scheme 19.

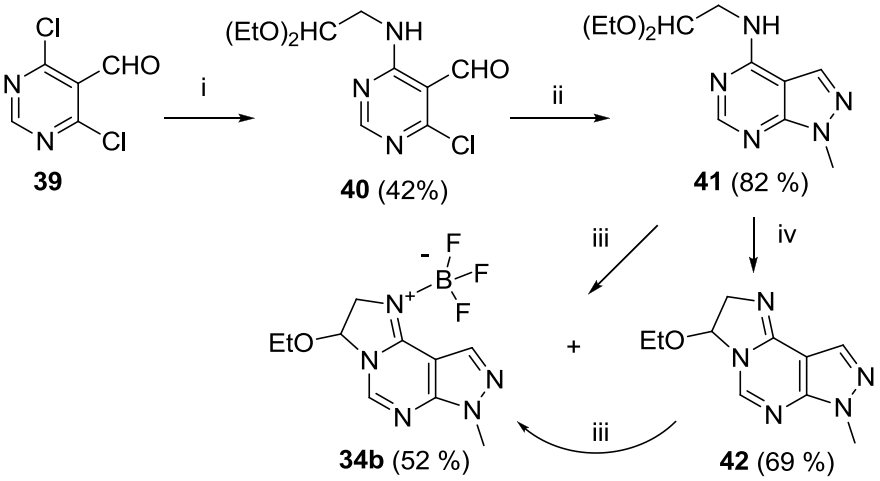
Another possibility to modify 2,3-dihydroimidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidines is aromatization. Aromatic imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine **38** may be obtained by the removal of ethanol molecule. This can be achieved by treating compound **21** with conc. sulphuric acid. Compound **38** is also formed when these conditions are applied to pyrazolo[3,4-*d*]pyrimidine **20**.



i: H_2SO_4, 80 °C, 30 min.

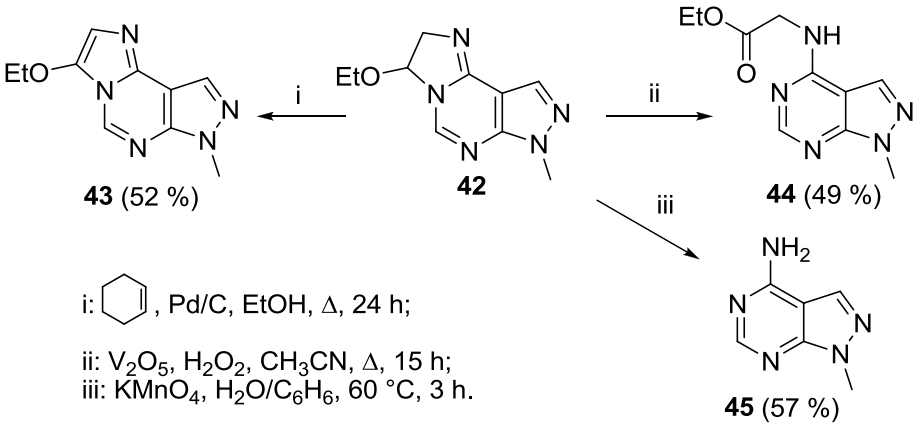
Scheme 20.

Oxidative conditions must be applied for the aromatization of compound **21** when functional group in imidazole ring has to be preserved. However, this compound might undergo side reactions in oxidative conditions, since it possess a sensitive methylthio group. In order to prevent side-reactions in further aromatization, analogue of compound **21** free of methylthio group was synthesized. Pyrazolo[3,4-*d*]pyrimidine **41** was synthesized by two step reaction from pyrimidine **39**. However, the mixture of compounds **42** and **34b** was formed when pyrazolo[3,4-*d*]pyrimidine was treated with boron trifluoride. Thus, for the cyclization of this compound to 2,3-dihydroimidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine **42** titanium tetrachloride was used as acidic component.



Scheme 21.

Aromatization of compound **42** was achieved with cyclohexene when palladium on charcoal was used as a catalyst. Imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine **43** was formed in this reaction in a moderate yield. Moreover, methods for the oxidation of *O,O*-acetal group were applied for compound **42**. Reaction with vanadium pentoxide and hydrogen peroxide mixture proceeded with opening of imidazole ring and oxidation forming compound **44**. Imidazole ring destruction also occurred when strong oxidizing agent – potassium permanganate was used. 4-Aminopyrazolo[3,4-*d*]pyrimidine **45** was formed in this reaction.



Scheme 22.

In summary, methods for the preparation of *peri*-fused pyrazolo[3,4-*d*]pyrimidines were proposed. The versatile method for the synthesis of 3-ethoxy-2,3-dihydroimidazo[1,2-*c*]pyrimidines has been developed. However, further modification of *N,O*-acetal moiety formed in this reaction is rather complicated.

Conclusions

1. 1,2,3,5,6,9-Hexaazabenz[*cd*]azulene, 6-thia-1,2,3,5,9-pentaazabenz[*cd*]azulene and 1,2,3,5,6,7,9-heptazazbenz[*cd*]azulene heterosystems are formed in reaction of 3-amino-4-chloro-1-methyl-6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidine with compounds possessing electrophilic and nucleophilic centers. *Orto*-fused imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine, instead of *orto*- and *peri*-fused heterosystem was formed when *O,O*-acetal group was used as electrophilic centre for the intramolecular cyclisation.
2. 4-(2,2-Diethoxyethyl)aminopyrimidines undergo cyclization to 2,3-dihydroimidazo[1,2-*c*]pyrimidinium salts when treated with boron trifluoride. These salts may form neutral 2,3-dihydroimidazo[1,2-*c*]pyrimidines or 4-(2-oxoethyl)aminopyrimidines depending on the aqueous base used.
3. The cyclization reaction of 4-(2,2-diethoxyethyl)aminopyrimidines to 2,3-dihydroimidazo[1,2-*c*]pyrimidines tolerates amino, methylthio, cyano, formyl groups. The rate of the reaction is reduced when electron-donating groups (alkoxy, alkylamino) are present at the 6-position of pyrimidine.
4. The substitution of nucleofuges with hydroxyl groups in pyrimidine ring takes place when imidazo[1,2-*c*]pyrimidinium salts containing strong electron-withdrawing groups or salts without labile hydrogen atom are treated with sodium hydroxide solution.
5. The functionalization of 3-ethoxy-7-methyl-5-methylthio-2,7-dihydro-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine is limited. The replacement of the ethoxy group, in the presence of acidic agent – titanium tetrachloride, was achieved only when benzyl thiol was used as a nucleophile. The aromatization of imidazole ring may be achieved by dehydrogenation with palladium on charcoal as catalyst. Ethoxy group remains unchanged in this reaction.

Summary in Lithuanian

Heterociklų chemijos vystymasis turi didelę reikšmę įvairioms mokslo sritims ir pramonės raidai. Pagrindinis šios chemijos srities uždavinys – kurti naujus heterociklinių junginių sintezės metodus, leidžiančius paprasčiau, efektyviau gauti norimos struktūros junginius. Tai apima ne tik heterociklų formavimo būdus, bet ir jų funkcionalizavimą, leidžiantį sukurti įvairiomis cheminėmis ir fizikinėmis savybėmis pasižyminčių junginių įvairovę. Šios mokslo srities pasiekimai pritaikomi biochemijoje, farmacijoje, fotofizikoje ir kitose mokslo ir pramonės šakose. Šiame darbe buvo siekiama sukurti efektyvius heterosistemų sintezės būdus, kuriuos galima pritaikyti pirazolo[3,4-*d*]pirimidino fragmentą turinčių heterociklų formavimui.

Šio darbo metu iš 3-amino-4-chlor-1-metil-6-metiltio-1*H*-pirazolo[3,4-*d*]pirimidino susintetintos trys naujos *orto*- ir *peri*-kondensuotosios heterociklinės sistemos. Surastos tinkamos sąlygos 4-(2,2-dietoksietilamino)pirimidinų ciklizacijai į 3-etoksi-2,3-dihidroimidazo[1,2-*c*]pirimidinus. Parodyta, kad tarpinius šių reakcijų produktus – 2,3-dihidroimidazo[1,2-*c*]pirimidinio druskas – veikiant vandeninėmis bazėmis galima suformuoti neutralius 2,3-dihidroimidazo[1,2-*c*]pirimidinus arba 4-(2-oksoetil)aminopirimidinus. Ištirta pirimidino žiede esančių pakaitų įtaka šiai reakcijai. Parodyta, kad ši ciklizacija sklandžiai vyksta substrate esant tokioms funkcinėms grupėms kaip alkiltio-, cian-, amino-, formilgrupės. Šią reakciją lėtina 6-oje pirimidino padėtyje esantys elektronų donoriniai (alkoksi, alkilamino) pakaitai. Parodyta, kad imidazo[1,2-c]pirimidinio druskas, turinčias stiprių elektronų akceptorinių grupių pirimidino žiede arba neturinčių lengvai atskylančio protono imidazolo žiede, veikiant vandeniniu natrio hidroksidu vyksta pirimidino žiede esančių nukleofugų pakeitimas hidroksigrupėmis. Nustatyta, kad 3-etoksi-7-metil-2,7-dihidro-3*H*-imidazo[1,2-*c*]pirazolo[4,3-*e*]pirimidinų funkcionalizavimo galimybės yra ribotos. Etoksigrupės pakeitimas, rūgštiniu komponentu naudojant titano tetrachloridą, sėkmingai vyko nukleofilu naudojant tik benziltiolį. Atliekant dehidrinimą cikloheksenu, esant paladžiui and anglies, vyksta imidazolo žiedo aromatizacija išliekant etoksigrupei.

List of publications

Publications in the journals covered in Web of Science:

1. V. Masevicius, R. Juskenas, S. Tumkevicius. Synthesis of a novel heterocyclic system – pyrazolo[5,4,3-*de*]pyrimido[4,5-*e*][1,4]diazepine. *Chem. Heterocycl. Compd.*, 2007, **43**, p. 1593.
2. V. Masevicius, R. Juskenas, S. Tumkevicius. Synthesis of novel pyrazolo[3,4-*d*]pyrimidines *peri*-fused with 1,4-diazepine, 1,4-thiazepine, and 1,2,4-triazepine rings. *J. Heterocycl. Chem.*, 2012, **49**, p. 315.
3. R. Juskenas, V. Masevicius, S. Tumkevicius. Reactivity of the pyrimidine nitrogen atom toward an acetal moiety: formation of 3-ethoxy-2,3-dihydroimidazo[1,2-*c*]pyrimidines by intramolecular cyclization of *N*-(2,2-diethoxyethyl)pyrimidine-4-amines. *Synthesis*, 2013, **45**, p. 2438.

Publications in international and lithuanian conference proceedings:

1. R. Juskenas, V. Masevicius, S. Tumkevicius. Formation of cyclic *N*,*O*-acetals involving pyrimidine nitrogen. International Conference on Organic Synthesis *"Balticum Organicum Syntheticum 2010"*. Riga, Latvia, June 27-30, **2010**, p. 106.
2. R. Juškėnas, V. Masevičius, S. Tumkevičius. Formation of 3-ethoxyimidazo[1,2-*c*]pyrimidinium salts and their reactivity towards nucleophiles. International Conference on Organic Synthesis *"Balticum Organicum Syntheticum 2012"* Tallinn, Estonia, July 1-4, **2012**, p. 132.
3. E. Vaičiūnaitė, R. Juškėnas, V. Masevičius. *N,O*-Acetalinį fragmentą turinčių imidazo[1,2-*c*]pirimidinio druskų sintezė ir savybių tyrimas. Mokslinė konferencija *"Organinė chemija"*. Kaunas, Lietuva, pranešimų medžiaga, balandžio 24 d., **2013**, 43.

Curriculum vitae

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