Olga B. Riabova[1], Vadim A. Makarov[1], Vladimir G. Granik[1], Cyril Párkányi*[2]

[1]State Research Center for Antibiotics, Nagatinskaya str 3a, 117105 Moscow, Russia
[2]Department of Chemistry and Biochemistry, Florida Atlantic University, 777 Glades Road, P.O. Box 3091, Boca-Raton, FL 33431-0991, USA
E-mail: parkanyi@fau.edu
Received July 3, 2007

J. Heterocyclic Chem., **45**, 62621 (2008).

1. Introduction.

Pyrimidines are the most abundant diazines. Pyrimidine derivatives, such as pyrimidine-2,4-dione (uracil), 5-methylpyrimidine-2,4-dione (thymine), and 4-amino-pyrimidin-2-one (cytosine), are the constituents of nucleic acids. Thiamine (vitamin B_1) is one of the examples of naturally occurring biologically active pyrimidines. A number of substituted pyrimidines were proven to be effective pharmaceuticals, examples of which include antihypertensive drugs, such as moxonidine, antibacterial agents, such as sulfamonomethoxine and sulfadimethoxine, antiepileptic drugs, such as phenobarbital, antitumor drugs, such as fluorouracil, and some other compounds.

The most important characteristic of the pyrimidine ring is a high degree of electron deficiency. Thus, the basicity constant pK_a of unsubstituted pyrimidine is equal to 1.3, *i.e.* it is four orders of magnitude lower than that of pyridine ($pK_a = 5.2$). This decrease in basicity results from destabilization of the cation, which, in turn, is caused by electron-withdrawing effect of the second nitrogen atom of the ring.

The above-mentioned electron-withdrawing effect of the nitrogen atoms is the principal reason why pyrimidine derivatives easily react with nucleophilic reactants. Such reactivity is enhanced by insertion of additional electron-withdrawing substituents, for example, a nitro group, into the pyrimidine ring.

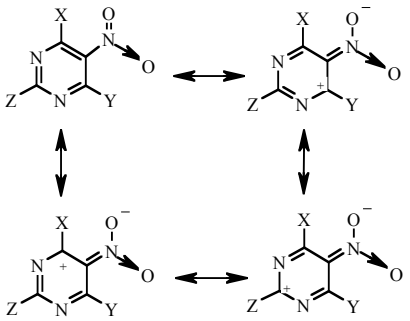
Thus, the use of 5-nitrosubstituted pyrimidines can represent a convenient route for the synthesis of a wide range of polysubstituted pyrimidines and other heterocyclic systems with potential biological activity.

When a nitro group is introduced into an electron deficient pyrimidine ring, it makes the resulting pyrimidine susceptible to a nucleophilic attack in the 2, 4 and 6 positions of the diazine cycle. These interactions furnish a convenient approach for preparation of various new pyrimidine derivatives with potential biological activity.

The nitro group, as well as some other powerful electron-withdrawing substituents, facilitates the ring opening by nucleophilic reagents, which can provide a convenient method for directional syntheses of heterocyclic compounds with potential physiological activity.

Detailed reviews of nucleophilic substitution in halogenated 5-nitropyrimidines can be found in several publications [1-4]. The majority of these papers discuss interactions between chlorinated 5-nitropyrimidines and various amines that result in formation of compounds independently substituted at the 2, 4 and 6 positions by amino, alkylamino, dialkylamino, and arylamino groups [5,6]. Also a number of amino derivatives containing one or two methylthio substituents have been reported [7,8]. Publication [9] reports preparation of symmetrical derivatives containing two 4-chloro-5-nitropyrimidine moieties connected *via* a diaminoalkyl fragment, for example, piperazine or 3,12-diaza-6,9-diazoniadispiro-[5.2.5.2]hexadecane moiety, attached to position 6 of the pyrimidine ring. Preparation of 5-nitropyrimidines containing either a substituted or unsubstituted hydrazine group has also been thoroughly investigated [10]. 4-Guanidino-5-nitropyrimidine derivatives containing chlorine atom or amino group in the position 6 of the ring have also generated a great interest [11]. Publication [3] exemplifies several instances of replacing a chlorine substituent by a fluorine atom in 4,6-dichloro- and 2,4,6-trichloro-5-nitropyrimidines using silver fluoride and triethylamine hydrofluoride.

Scheme 1



Recently, however, the majority of publications reporting reactions of 5-nitropyrimidines have been devoted either to reduction of the nitro group that made it possible to synthesize various bicyclic compounds, or to the opening and subsequent re-closure of the pyrimidine ring.

The present review deals with the literature published after 1991, when the most recent similar review [12] was published.

2. Preparation of condensed heterocyclic systems by means of reducing the nitro group in 5-nitropyrimidines.

It is known that analogs of purine bases can possess antiviral and antitumor activity; thus, methods of preparation of these compounds bearing various functional substituents have recently become very important. The scope of studies devoted to development of preparation methods for obtaining various natural compounds and alkaloids encompassing condensed pyrimidine rings are continuously expanding. The reports cited below show that the use of polysubstituted 5-nitropyrimidines as starting compounds and reduction of their nitro group lead to a wide range of bicyclic systems containing pyrimidine ring.

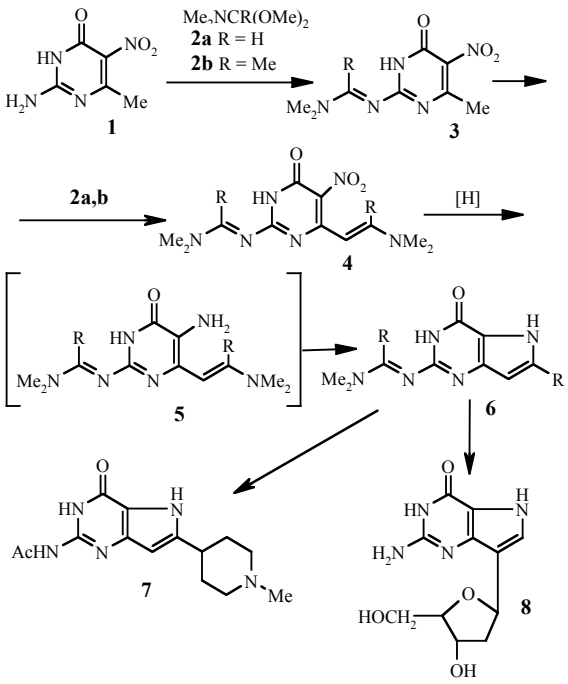
2.1. Annulation of five-membered rings.

2.1.1. Synthesis of pyrrolo[3,2-*d*]pyrimidines. According to most publications, reduction of a nitro group in pyrimidines is accompanied by formation of a new ring. This process is reported to result in the formation of a pyrrole ring and a bicyclic system of pyrrolo[3,2-*d*]-pyrimidine.

Convenient starting compounds for preparation of pyrrolo[3,2-*d*]pyrimidines are pyrimidines bearing a methyl group in the position 6 of the ring. Electron-withdrawing properties of the pyrimidine ring itself in combination with the electron-withdrawing effect of nitro group in the *ortho*position enhance activation of this methyl group that facilitates formation of the corresponding carbanion, which readily reacts with various electrophilic reactants. Such reactions can be exemplified by condensation of the corresponding methylnitropyrimidines with various amide acetals. Alkoxy anion, being formed in such an equilibrium mixture [13], promotes removal of a proton from the methyl group, and the resulting anion attaches itself to the *meso*-position of the immonium cation, the process being accompanied by elimination of a molecule of an alcohol.

The above method of preparing pyrrolo[3,2-*d*]-pyrimidine derivatives starting from 2-amino-4-oxo-6-methyl-5-nitropyrimidine **1** was described in a series of publications [14-19]. Interaction between compound **1** and dimethylformamide acetals **2a** or dimethylacetamide acetals **2b** proceeds smoothly and gives rise to the corresponding derivatives **4**. It was shown [15,17] that the reaction starts with a condensation of the acetal with a free amino group of the pyrimidine. Formation of enamine **4** from the resulting amidine **3** occurs under the action of amide acetal upon the activated methyl group. Subsequent reduction of the nitro group in the enamine **4** leads to a ring closure and formation of pyrrolopyrimidine **6** (Leimgruber-Batcho reaction) [20,21]. In some experiments alkylation of the pyrimidine NH-group was also observed; this observation is supported by well-known alkylating properties of amide acetals [22]. The key step in this synthesis is the reduction of the nitro group, which can be accomplished by different means, for example, by sodium thiosulfate [15,17-19], or by means of hydrogenation in the presence of palladium on charcoal [14] or palladium hydroxide [16]. It should be pointed out that formation of the pyrrole ring occurs spontaneously during the reduction. The resulting pyrrolo[3,2-*d*]pyrimidine **6** was subjected to a series of subsequent reactions to form compound **7**, which is a selective inhibitor of 5-HT_{1F} receptors, and nucleoside **8**, which displays antitumor activity [15].

Scheme 2



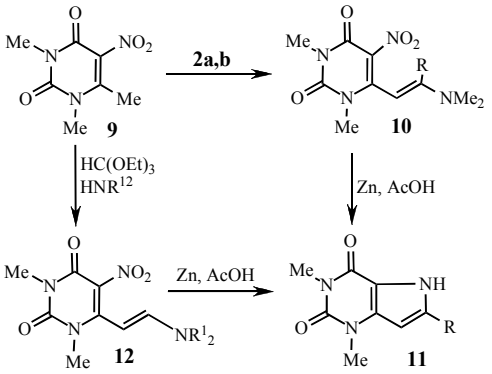
Interaction of 1,3,6-trimethyluracil **9** and amide acetals **2a,b** proceeds in an analogous manner and results in formation of compound **10**; reduction of the nitro compound **10** with zinc and acetic acid results in cyclization and formation of bicyclic pyrrolopyrimidinone **11** [23]. When dimethylformamide acetal **2a** is used as a starting material, the yield of the product is 65%, while using dimethylacetamide acetal **2b** gives only about a half of this yield.

Similar transformations accompanying hydrogenation of the nitro compound on Pd/C are reported in publication [24].

Reactions of trimethyluracil with a mixture of orthoformic ester and various secondary amines were also studied [25]. This interaction made it possible to obtain a

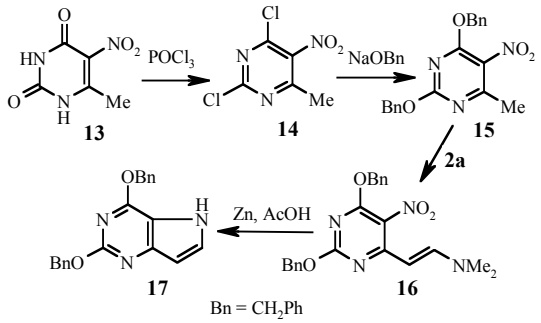
number of miscellaneous substituted enamines **12** that had been difficult to synthesize previously due to a necessity of preparing the corresponding starting acetals (Scheme 3). Pyrrolopyrimidinones **11** were shown to be easily obtained *via* reduction of compounds **12** with zinc and acetic acid.

Scheme 3



6-Methyl-5-nitrouracil **13** was used as a starting material to prepare the immuciline analog **17** [26], which is a selective inhibitor of purine nucleoside phosphorylase.

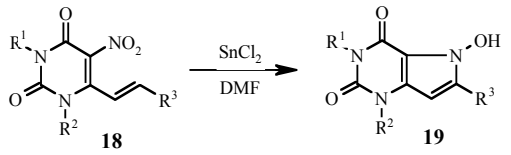
Scheme 4



The synthesis involved treatment of nitrouracil **13** with phosphorus oxychloride and resulted in the dichloro compound **14**, which then reacted with sodium benzyloxide to form O,O-dibenzyl derivative **15**. The latter reacted with dimethylformamide acetal **2a** giving rise to enamine **16**. Reduction of this enamine with zinc and acetic acid accompanied by a ring closure gave pyrrolopyrimidine **17** in a 78% yield (Scheme 4).

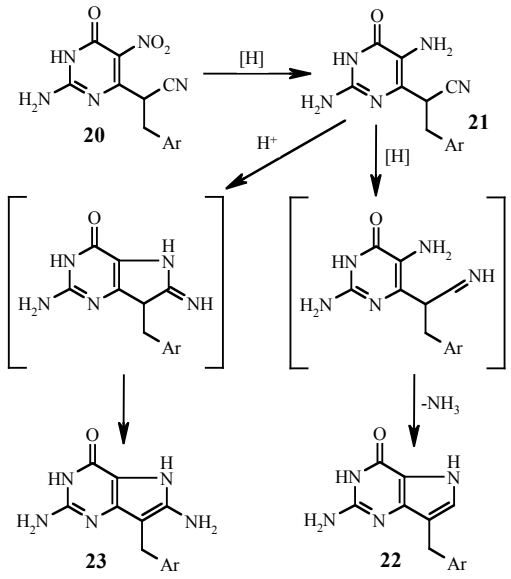
High yields of 7-hydroxy-8-substituted-9-desazaxanthines **19** were obtained *via* reduction of 5-nitro-1,3-dialkyl-6-styryl(furoyl, thienyl, vinyl)uracils **18** with tin chloride in dimethylformamide [27].

Scheme 5



Unexpected transformations accompanying analogous preparation of pyrrolo[3,2-*d*]pyrimidines have been reported [28-29]. It was shown that the reduction of the nitro group with Raney nickel in acetic acid [28] or with sodium thiosulfate [29] led to 5-aminopyrimidines **20**, which further underwent a partial reduction of cyano group with formation of an intermediate imino derivative.

Scheme 6

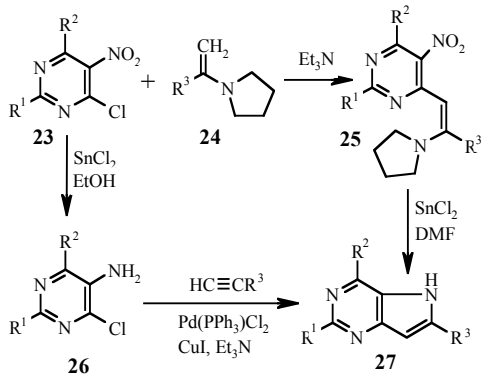


This intermediate underwent a ring closure to form the target bicyclic products **22** containing no amino group in the pyrrole ring (Scheme 6). Acidic treatment of compound **21** caused pyrrole cyclization to occur. The ring closure involved a primary amino group and a nitrile group and resulted in formation of aminopyrrolopyrimidines **23** [30]. We suppose that the processes involved here can be satisfactorily described by the transformations on Scheme 6.

Two original methods of preparing 6-substituted pyrrolo[3,2-*d*]pyrimidines **27** are described in [31]. The authors showed that 4-chloro-5-nitropyrimidines **23** could act as arylating agents toward enamines. Interaction of chloro derivatives **23** with substituted enamines **24** was stated to proceed *via* heteroarylation of β-position of enamine (heating in toluene in the presence of triethylamine) to form compounds **25**. Subsequent reduction of enaminopyrimidines **25** resulted in ring closure and formation of pyrrolopyrimidines **27** (Scheme 7). The investigators also found another route to obtain

compounds **27** *via* a preliminary reduction of nitro group in compounds **23**. The resulting 5-amino derivatives **26** reacted with acetylenes in the presence of triphenylphosphine palladium dichloride to form pyrrolopyrimidines **27**.

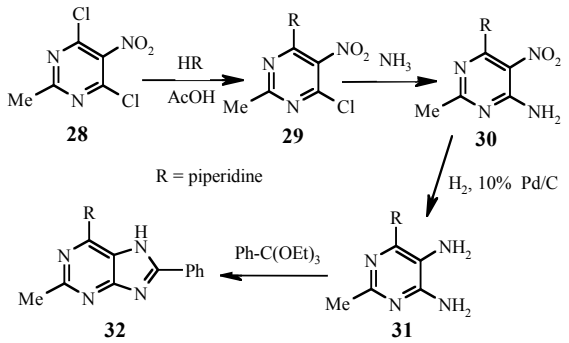
Scheme 7



2.1.2. Preparation of purine derivatives. The use of 5-nitropyrimidines as starting compounds is a well-known and reliable method of preparing substituted purines including their various analogs and purine base derivatives, as well as a number of naturally occurring compounds containing bicyclic imidazo[4,5-*d*]pyrimidine structure. A series of articles covering newly discovered transformations of the above type appeared during the last two decades.

Publication [31] reports synthesis of 2-methyl-8-phenyl-6-piperidinopurine **32** comprising the following reaction sequence starting from 4,6-dichloro-2-methyl-5-nitropyrimidine **28**: replacement of one of the chlorine atoms by a piperidine moiety and another one by an amino group, hydrogenation of the nitro group in the presence of palladium on charcoal followed by interaction of the product with triethyl orthobenzoate resulting in formation of the target product **32**.

Scheme 8



Authors of publications [32,33] to prepare an analog of the antitumor antibiotic drug spicamycin **34** used similar transformations (Scheme 9). The first stage of the synthesis consisted of condensation of the free 4-amino group in the pyrimidine **33** with orthoformic ester; after its completion the nitro group of the intermediate was hydrogenated on Pd/C, the reduction being accompanied by imidazole ring formation.

Scheme 9

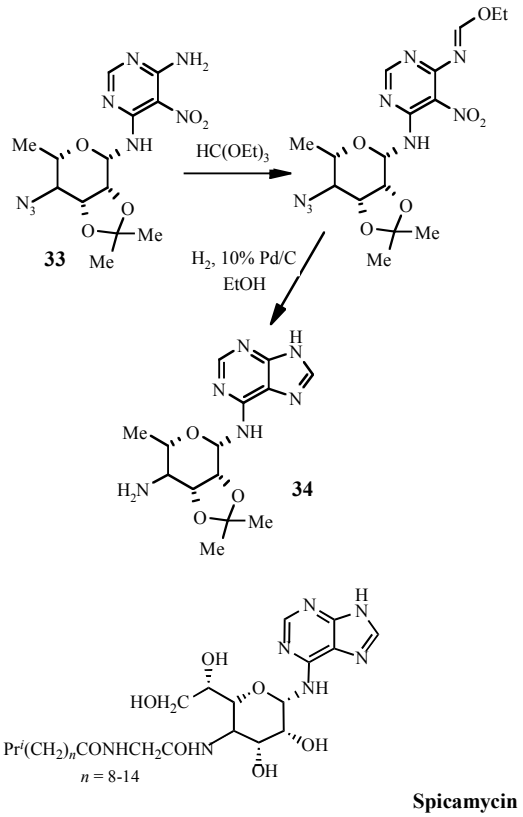
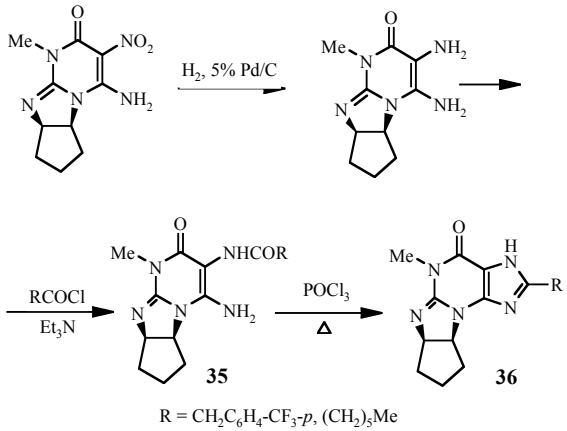


Figure 1

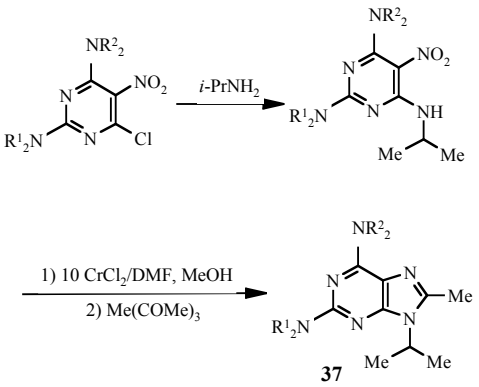
A method for preparation of tetracyclic guanine derivatives **36**, which are inhibitors of phosphodiesterase, has been reported in publication [34]. Here the imidazole ring was formed by reaction of phosphorus oxychloride with intermediate **35** (Scheme 10).

Scheme 10



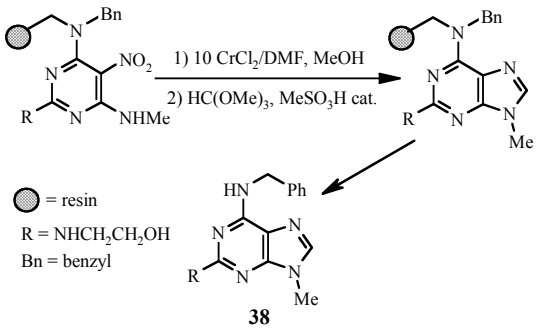
5-Nitro-6-chloropyrimidines are used in directional synthesis of 9-substituted purines. Traditional preparative methods involve the first step comprising imidazole ring closure and a subsequent alkylation step. Separation of the resulting mixture of isomers is usually difficult due to the fact that both the positions 7 and 9 of the compound undergo alkylation. When 6-chloropyrimidines are used in this reaction (Scheme 11), it is necessary to replace their chlorine atom by a primary amino group before imidazole cyclization. This method of preparation gives rise exclusively to 9-substituted purines. This approach was followed in a number of publications [35-37]. Thus, selective preparation of the 9-isopropylpurine derivative **37** [37] was accomplished by means of the Miller method. The method comprises application of a reducing agent such as a tenfold excess of chromium dichloride. The yield of the product was 85%.

Scheme 11



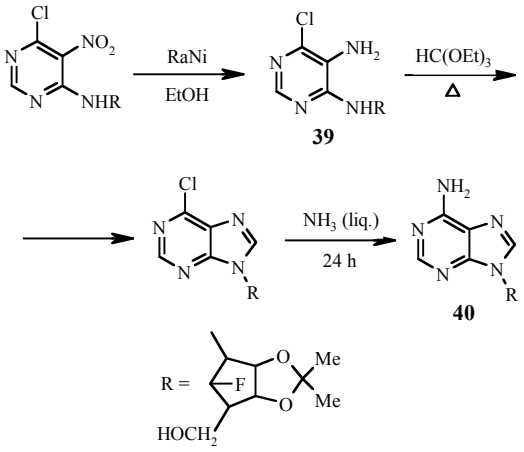
A similar approach is described in [36], which reports preparation of the synthetic antibiotic olomoucin **38** using a solid phase synthesis technique (Scheme 12).

Scheme 12



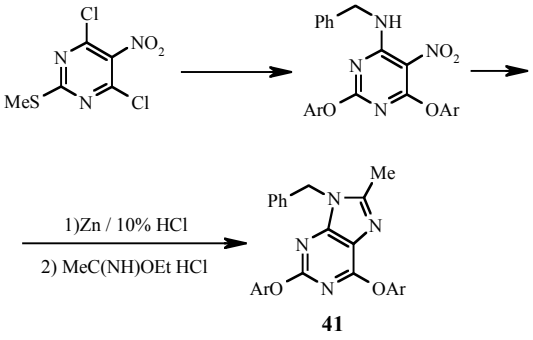
Hydrogenation of the nitro group using Raney nickel was employed in directional synthesis of a fluorinated nucleoside analog **40** [35]. The yield of the corresponding diaminopyrimidine **39** was 62%. The yield of the imidazole, which was formed *via* interaction with orthoformic ester, was 97% (Scheme 13).

Scheme 13



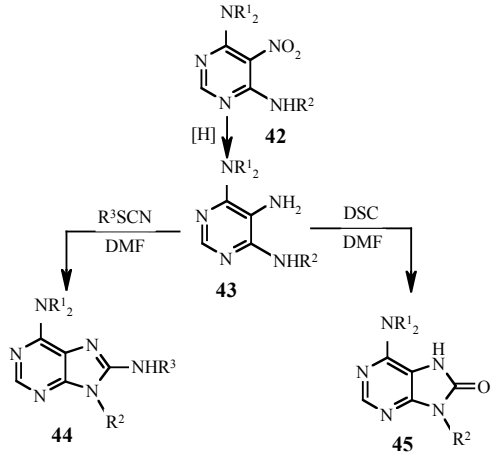
Authors of [38] described preparation of 9-substituted purines **41** inhibiting one of the blood coagulability factors (Scheme 14). The reduction was conducted with zinc and hydrochloric acid, and the subsequent ring closure of the imidazole ring was effected using ethyl acetimidate hydrochloride under severe conditions.

Scheme 14



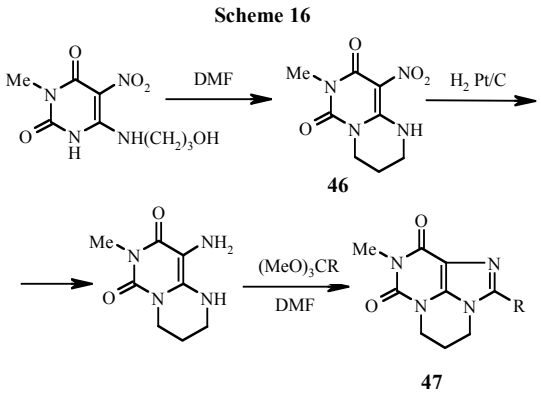
A method for preparation of 9-substituted purines is also described in publication [39]. The authors discussed a possibility of introducing a secondary amino group into position 8 of the imidazole ring **44** during this synthesis. The first step of the process included reduction of the 5-nitro group of pyrimidines **42**; then the resulting triaminopyrimidine **43** was reacted with thiocyanates in dimethylformamide. The publication also provides a method for the preparation of various 9-substituted 8-purinones **45**. This method includes using *N*,*N*'-disuccinimidylcarbonate (DSC) for the imidazole ring formation (Scheme 15).

Scheme 15



A tricyclic purine derivative **47** was synthesized *via* a sequence of transformations involving formation of a saturated pyrimidine ring (Scheme 16), reduction of the nitro group, and imidazole ring closure under the action of orthoformic ester [40].

Scheme 16

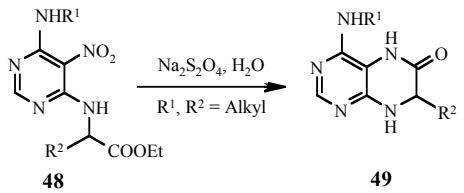


2.2. Annulation of six-membered rings

2.2.1. Preparation of pteridine derivatives. Only a limited number of publications have been devoted to the preparation of pteridines *via* reduction of the nitro group in 5-nitropyrimidines.

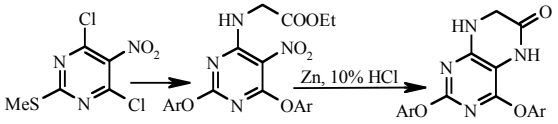
According to publication [39], reduction of a nitro group in pyrimidines **48**, which contain an α-aminoester moiety in position 4, is accompanied by a closure of the piperazine ring and formation of a pteridine system. The yields of resulting pteridines **49** exceeded 60%.

Scheme 17



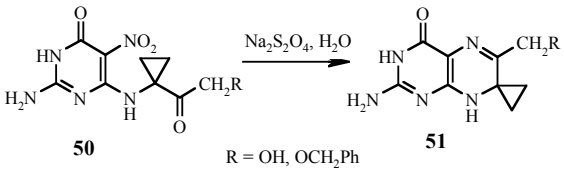
Similar cyclization involving interaction between an amino group and a carbethoxy moiety is described in [38]. Formation of piperazine ring occurs with very good yields (Scheme 18).

Scheme 18



Preparation of two new pteridine-7-spirocyclopropanes **51**, which are irreversible inhibitors of dihydrofolate reductase, was accomplished *via* reduction of the nitro group in compound **50** with sodium thiosulfate [41]. This reaction was accompanied by spontaneous formation of dihydropyrazine ring leading to the target products (Scheme 19).

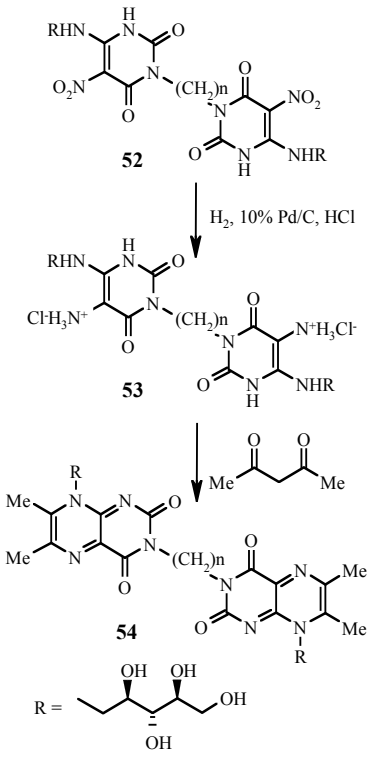
Scheme 19



Preparation of a symmetrical compound **54** with a complex structure including two pteridine moieties was started by hydrogenation of nitro group in position 5 of pyrimidine **52** in the presence of palladium on charcoal [42]. The authors succeeded in isolating the intermediate hydrochloride **53**, which was subsequently reacted with acetylacetone. The process (Scheme 20) was also shown to be a one-pot synthesis that can spare investigators the necessity to isolate the corresponding hydrochloride. It is interesting to note that a dihydropyrazine ring closure occurs even at ambient temperature.

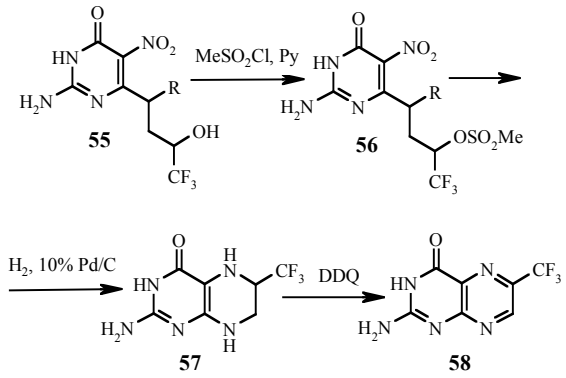
Taking into account a great interest in various fluorine-containing heterocyclic compounds, the authors of [43] attempted to prepare 6-trifluoromethylpterin **58**. A standard route for preparation of pteridines starting from 5-nitro- or 5-aminopyrimidines, as it has been already mentioned above, comprises cyclization involving the carbonyl group of the side chain of the molecule. However, recently considerable efforts have been directed to the piperazine ring closure with participation of hydroxyl group. However, the investigators failed to a determine the conditions of this transformation. Nevertheless, the authors of [43] proposed an original method, which allowed them to utilize hydroxyl groups without their preliminary oxidation. 5-Nitropyrimidine **55** was chosen as the starting compound. It was treated with

Scheme 20



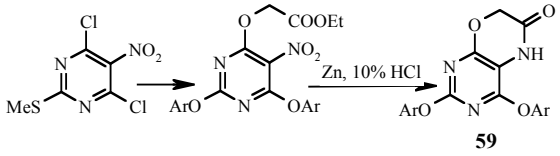
methanesulfonyl chloride in pyridine and the resulting product **56** was hydrogenated in the presence of palladium on charcoal. The hydrogenation was accompanied by formation of a saturated pyrazine ring **57**, which was then dehydrogenated with dichlorodicyanoquinone. However, the yield of the target bicyclic compound **58** was only 28% (Scheme 21).

Scheme 21



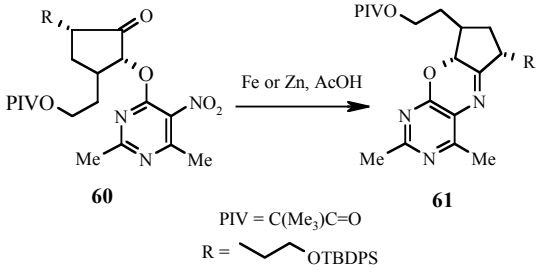
2.2.2. Preparation of pyrimido[4,5-*b*][1,4]oxazine derivatives. The authors of the already mentioned publication [38] showed that reduction of a nitro group in the corresponding pyrimidines can give rise to imidazole and piperazine derivatives and, moreover, it can also result in formation of 1,4-oxazines **59** with the yields exceeding 90% (Scheme 22).

Scheme 22



In the course of a search for new antimetastatic non-peptide agents the authors of [44] used a known method of reducing the intermediate **60** nitro group with iron filings or zinc powder in acetic acid (Scheme 23). The reduction was accompanied by spontaneous cyclization to an oxazine and formation of the tricyclic compound **61** in a 90% yield.

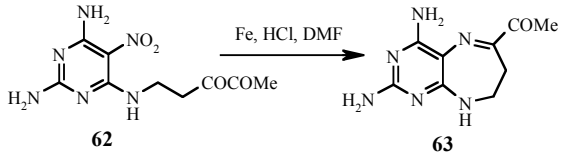
Scheme 23



2.3. Annulation of seven-membered rings

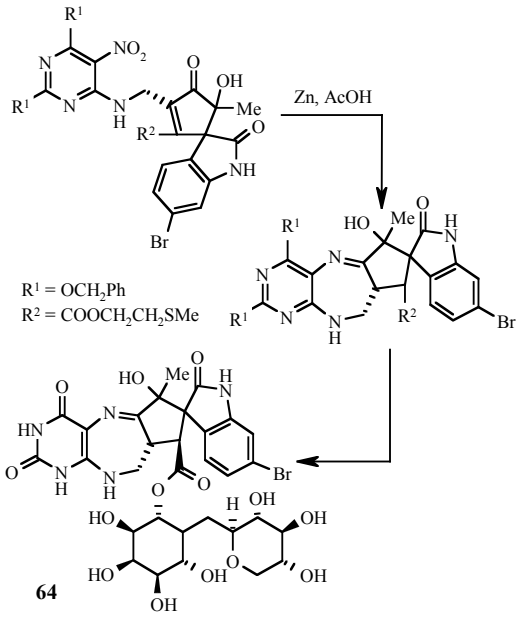
Publication [45] discusses the possibility of a diazepine ring closure *via* reduction of the nitro group in 2,4-diamino-6-(3,4-dioxopentylamino)-5-nitropyrimidine **62**. The optimum route was the reduction with iron powder in hydrochloric acid mixed with DMF to enhance the solubility of the starting compound. The reduction was followed by cyclization of the resulting amino intermediate. Duration of the reaction was 4 hours and the yield of the product pyrimido[4,5-*b*][1,4]diazepine **63** amounted to about 55% (Scheme 24).

Scheme 24



Similar formation of diazepine ring [46] involving participation of amino group of the pyrimidine and ketone group of its side chain was accomplished in the course of directional synthesis of the natural compound neosurugatoxin **64** (Scheme 25).

Scheme 25



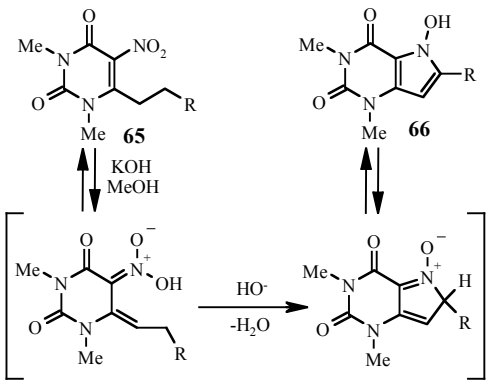
Similar formation of diazepine ring [46] involving participation of amino group of the pyrimidine and ketone group of its side chain was accomplished in the course of directional synthesis of the natural compound neosurugatoxin **64** (Scheme 25).

3. Utilization of 5-nitropyrimidines in preparation of condensed heterocyclic systems without involving the nitro group reduction

3.1. Formation of five-membered rings.

It was shown [24] that annulation of the pyrrole ring takes place under the action of potassium hydroxide methanol solution upon 5-nitropyrimidines **65** containing a $-CH_2CH_2-$ moiety in their side chain. The target pyrrolo[3,2-*d*]pyrimidines **66** containing 1-hydroxy group were isolated in 50-65% yields (Scheme 26).

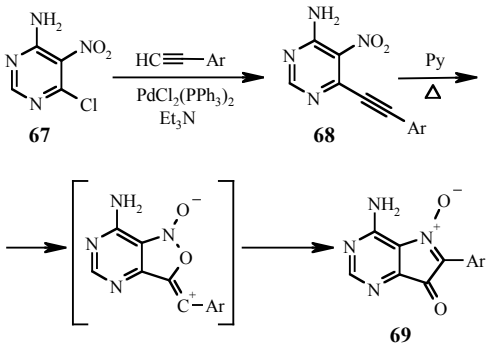
Scheme 26



A short and effective preparative method for obtaining good yields of pyrrolo[3,2-*d*]pyrimidines **69** (87-95%) was proposed in publication [47]. The first step of the method included the Sonogashira reaction, *i.e.* replacement of a chlorine atom in pyrimidine **67** with arylacetylene in the presence of triethylamine and a palladium catalyst (Scheme 27). When refluxed in pyridine, the resulting products **68** readily underwent a ring closure to form 5-oxides, which are difficult to synthesize by other methods.

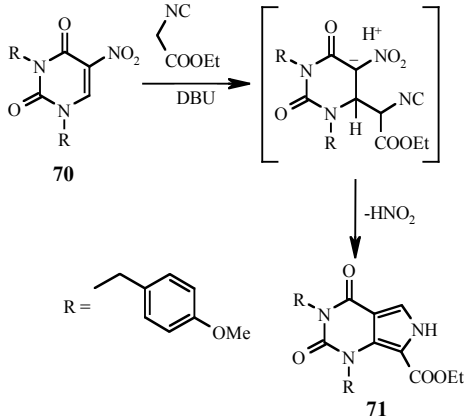
Reliable information concerning the mechanism of the cyclization shown below is not available in the literature, despite the fact that such an interesting process is worthy of thorough investigation. We think that the mechanism is similar to that of the cyclization described in the monograph [48], with an intermediate formation of an isoxazole derivative.

Scheme 27



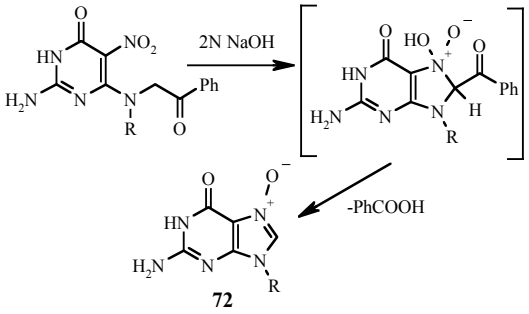
Another method for preparation of pyrrolopyrimidines is described in publication [49]. It is based on interaction of 5-nitrouracil **70** with isocyanoacetate in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU). The process (Scheme 28) is accompanied by the elimination of nitrous acid and the yield of the product pyrrolo[3,4-*d*]pyrimidine **71** is about 88%.

Scheme 28



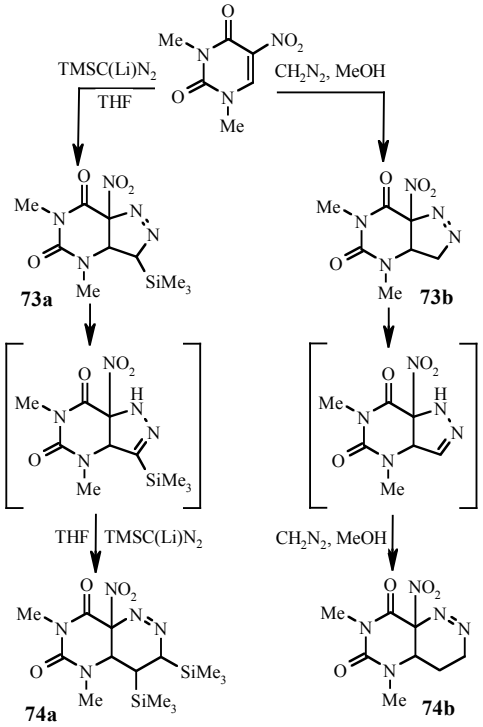
The authors of a number of publications [50-52] proposed a "phenacylamine route" to prepare a series of guanine derivatives showing antitumor activity. Thus, it was shown that the presence of a strong base promotes elimination of benzoic acid and cyclization of the imidazole ring to form 7-oxides **72** (Scheme 29).

Scheme 29



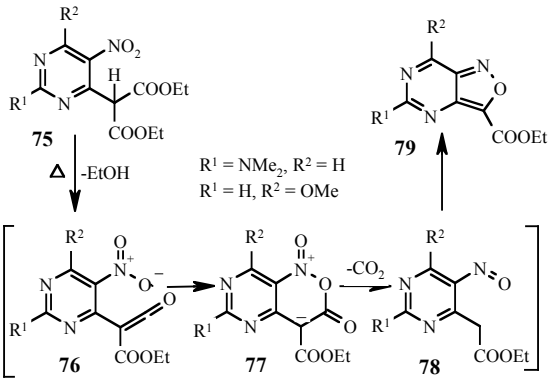
Other investigators [53] used classical synthons commonly applied in preparation of pyrazole cycles, namely, diazomethane and one of its derivatives (lithium trimethylsilyldiazomethane). This allowed them to obtain pyrazolo[4,3-*d*]pyrimidines **73a,b** without elimination of a nitro group and, consequently, the products of the synthesis contain a 7a-nitro group in their molecules. It should be noted that the reaction mixture also contained products comprising six-membered pyridazine rings cycles **74a,b**, which resulted from interaction between pyrazolo[4,3-*d*]pyrimidines **73a,b** and an excess of diazomethane (Scheme 30). However, the authors did not disclose details of the mechanism of their formation.

Scheme 30



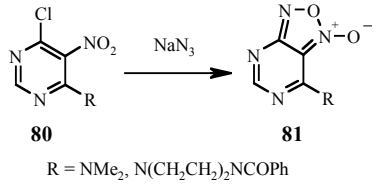
Preparation of substituted isoxazolo[4,3-*d*]pyrimidines **79** was accomplished on the basis of nitro derivatives **75** [54] obtained *via* interaction of *ortho*-chloronitropyrimidines and malonic ester. Heating of the compound **75** resulted in elimination of an alcohol molecule and formation of ketene **76** (Scheme 31). Analogous transformations for a series of diethylpropanedionates have been described [55]. Nucleophilic *ortho*-nitro group attacks a ketone group in the side chain leading to the formation of a bicyclic intermediate **77**. The latter eliminates CO_2 with formation of an *ortho*-nitrosocarbene **78**, which finally affords the target isoxazole **79**.

Scheme 31



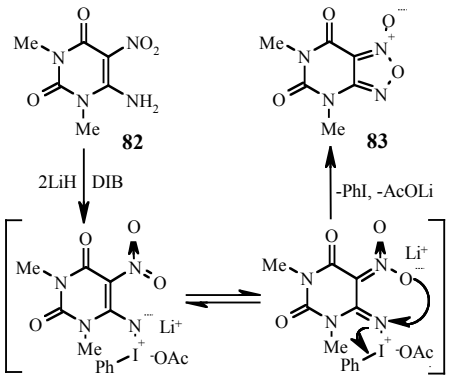
Furoxane derivatives are known to be exogenous donors of nitric oxide; thus, the authors of publication [56] attempted to synthesize [1,2,5]oxodiazolo[3,4-*d*]-pyrimidine-1-oxides **81**. These were prepared in good yields *via* reaction of chloronitropyrimidines **80** with sodium azide in dimethyl sulfoxide.

Scheme 32



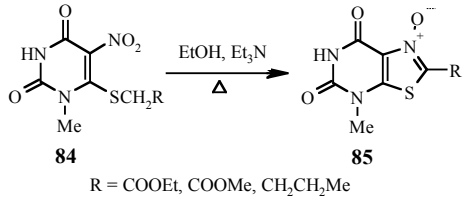
An unusual method for preparation of bicyclic N-oxides of [1,2,5]oxadiazoles **83** was proposed in work [57]. 6-Amino-5-nitro-1,3-dimethyluracil **82** was chosen as a starting material. It was reacted with iodosobenzoic acid diacetate in the presence of lithium hydride (Scheme 33). The yield of the product **83** was 95%.

Scheme 33



Heating 6-methylenethio derivatives **84** in alcohol in the presence of triethylamine gave a series of thiazolo-[4,5-*d*]pyrimidine N-oxides **85**, which are antagonists of the purine receptors [58].

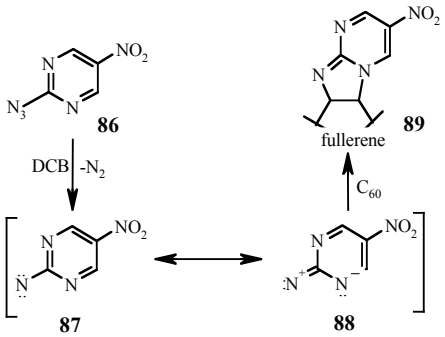
Scheme 34



R = COOEt, COOMe, CH_2CH_2Me

Preparation of a fullerene derivative containing 5-nitroimidazo[1,2-*a*]pyrimidine moiety **89** starting from 2-azidopyrimidine **86** was reported in [59]. During this reaction the azide decomposed into nitrene **87**, which, in turn, could isomerize to form 1,3-dipole **88**. During all the transformations the nitro group remained intact.

Scheme 35

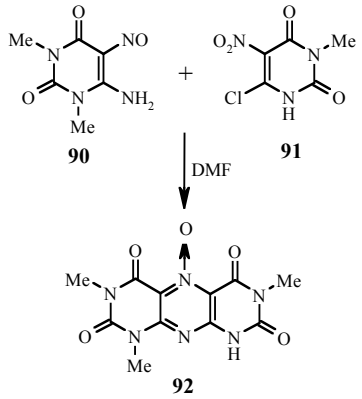


3.2. Formation of six-membered rings.

Among the reported data there are some papers disclosing participation of the 5-nitro group in the formation of new compounds with rarely encountered six-membered rings.

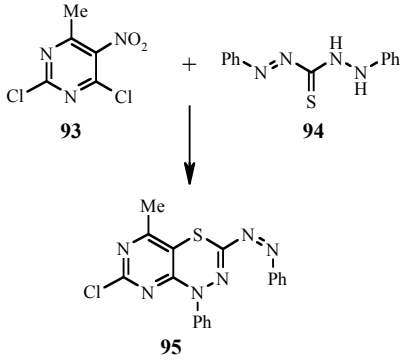
For example (Scheme 36), authors of [60] showed that interaction between 6-amino-5-nitrosopyrimidine **90** and 5-nitro-6-chloropyrimidine **91** in dimethylformamide resulted in formation of pyrazine ring, which led to a 35% yield of pteridine N-oxide **92**.

Scheme 36



Elimination of nitrous acid was also observed during interaction of 4-chloro-5-nitropyrimidine **93** with disubstituted thiosemicarbazide **94**. The product of the interaction was a [1,3,4]thiadiazine derivative **95** [61].

Scheme 37



4. Transformations of 5-nitropyrimidines involving the ring opening

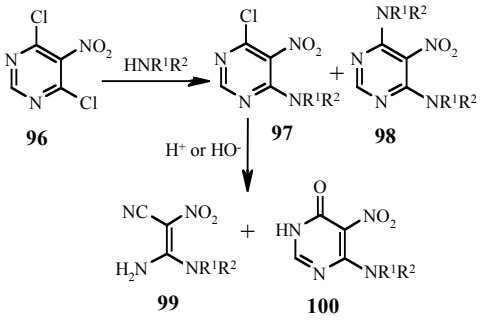
Many chemical transformations in 5-nitropyrimidine series are accompanied by opening of the pyrimidine ring. In the majority of cases the ring opening results in formation of various enamine derivatives, which can be isolated and characterized. These enamines can be transformed into various azaheterocycles under the action of miscellaneous reactants.

4.1. Reactions resulting in formation of acyclic enamine derivatives.

The most common route of opening the 5-nitropyrimidine ring involves hydrolysis of their N_1-C_2-

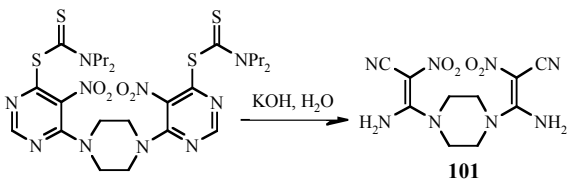
bond. Earlier it was shown that such hydrolysis can occur in either acidic or alkaline or neutral media [62-64] and transform 4-chloro-5-nitropyrimidine derivatives **97** into highly polarized nitroenediamines **99** (Scheme 38). Acidic hydrolysis provides better yields. The authors showed that this transformation is also valid for a considerable variety of 6-amino derivatives. On the other hand, attempts to prepare enediamines containing arylamino group in α-position of the enamine encountered considerable difficulties [65]. Deactivating influence of 6-arylamino group upon 4-chlorine atom is less pronounced than in the case of amino or alkylamino substituent and, hence, interaction between 4,6-dichloro-5-nitropyrimidine **96** and aromatic amines proceeds ambiguously, giving rise not only to the target chloropyrimidines, but also to 4,6-bisarylamino-5-nitropyrimidines **98**, which cannot undergo transformation into enamines. Preparative separation of pyrimidines **97** and **98** proved to be extremely difficult. Because of this the researchers subjected the mixture to reflux in hydrochloric acid that transformed chloropyrimidines **97** into enamines **99**, which could be easily separated from substituted pyrimidines **98** and **100.**

Scheme 38



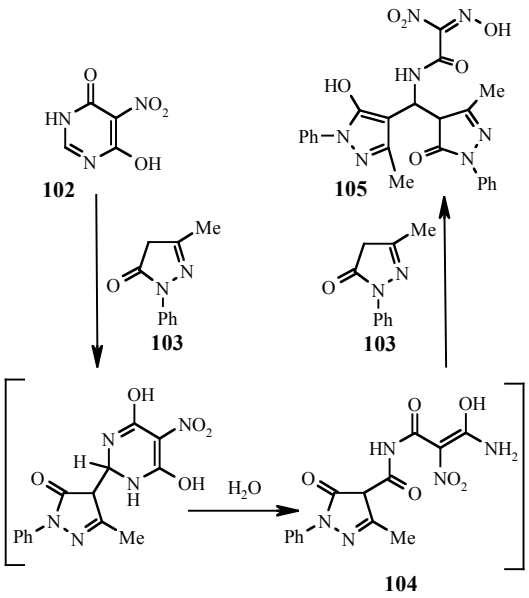
A similar cleavage of the pyrimidine ring with formation of highly polarized enamines **101** is described in publication [66]. However, in this case the position 4 of the starting compound contains a dithiocarbamic acid moiety instead of a chlorine atom (Scheme 39).

Scheme 39



Cleavage of the N_1-C_2 bond in the pyrimidine ring was also observed during interaction between 6-hydroxy-5-nitro-4(*3H*)-pyrimidinone **102** and pyrazolone **103** [67] (Scheme 40), with the nitroenamine derivative **104** implicated in the mechanism. Its reaction with another pyrazolone molecule resulted in the formation of dipyrazolylmethane **105** in a 31% yield.

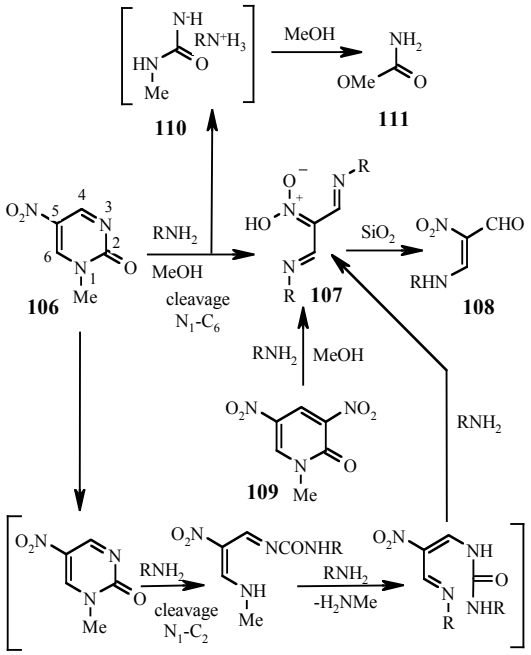
Scheme 40



Authors of [68] investigated the ring opening reaction of 1-methyl-5-nitro-2(*1H*-)pyrimidinone **106** initiated by the action of amines. The investigators postulated that reaction proceeded *via* cleavage of the N_1–C_6 bond of the pyrimidine (Scheme 41). The resulting intermediate exists as nitrodiimine **107** as proved by means of NMR. However, a different type of transformation of 2-oxopyrimidines has been described in the literature as well [69-71]. Compound **107** proved to be unstable in the presence of water and underwent hydrolysis to form aldehyde **108**. Secondary amines reacted differently; this was proved by NMR-monitoring of reaction mixtures formed in the reactions of morpholine. In this case morpholine attached itself either to the position 4 or to the position 6 of the pyrimidine.

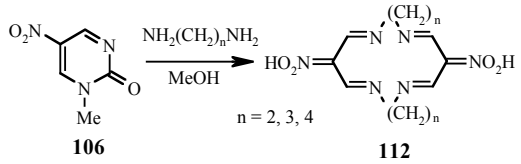
Recently the same authors succeeded in preparation of a similar diimine according to the reaction of 1-methyl-3,5-dinitro-2(1*H*)-pyridone **109** with primary amines in pyridine [72]. The reaction, however, was hindered by the low solubility of the pyridone that resulted in formation of a complex mixture and lowering of the yield of the target compound **107** (Scheme 41). According to the authors [68], solubility of a pyrimidinone in organic solvents is higher than that of a pyridine. The anion **110** with a low reactivity interacts with methanol to form a methyl carbamate. As a result, the yield of the target diimine **107** becomes considerably higher.

Scheme 41



Interactions between 1-methyl-2-oxo-5-nitropyrimidine **106** and diamines proceed along similar pathways (Scheme 42). However, they result in formation of dimers **112**.

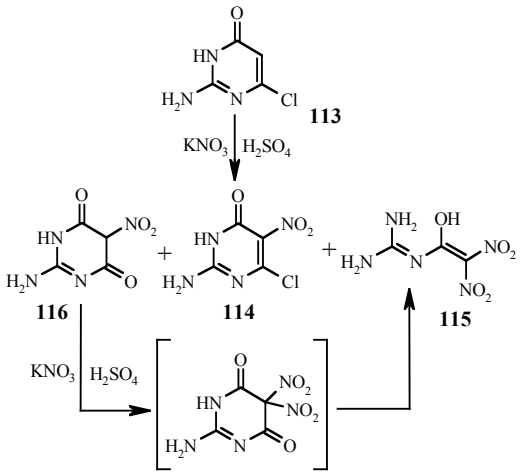
Scheme 42



Nitration of 2-amino-6-chloro-4-pyrimidinone **113** followed by storage of the reaction mixture for 10 hours resulted in formation of two products: the target nitropyrimidine **114** and another substance that was later isolated and identified as the dinitro derivative **115** [73]. Nitration of either chlorooxonitropyrimidine **114** or dioxonitropyrimidine **116** was shown to give 80% yield of the dinitro compound (Scheme 43). In this case N_1-C_6 bond of pyrimidine ring was broken. The resulting dinitro compound had an open-chain structure, which was proven by means of physicochemical analytical techniques.

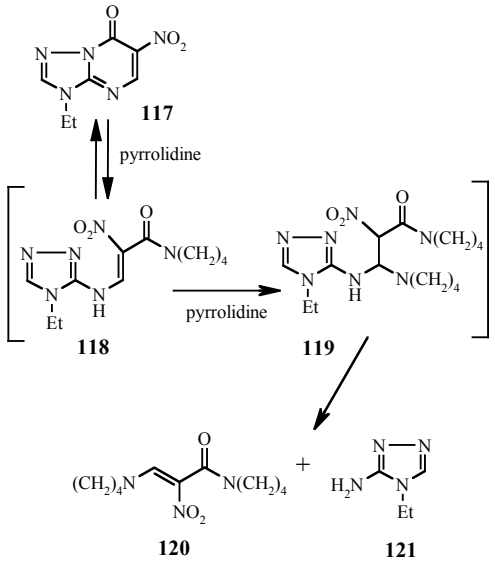
Several reports of splitting a condensed pyrimidine ring by nucleophilic reactants appeared in the published literature. Thus, the opening of the pyrimidine ring (Scheme 44) occurs during interaction between 6-nitro-3-ethyl-[1,2,4]-triazolo[1,5-*a*]pyrimidin-7-one **117** and pyrrolidine. The authors of [74] consider the first step of the process to be a reversible nucleophilic attack on the C_7

Scheme 43



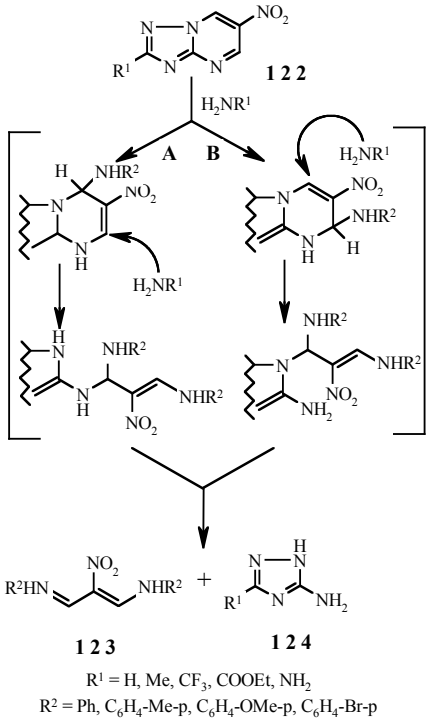
carbonyl carbon. Then the intermediate amide **118** reacts with the second amine molecule to form Michael adduct **119** that, in turn, decomposes into nitroacrylamide **120** and 3-amino-[1,2,4]-triazole **121**.

Scheme 44



Interaction of azolopyrimidines **122** with primary arylamines is accompanied by destruction of the pyrimidine ring and formation of acyclic 1-amino-2-nitro-3-iminopropene **123** and 5-aminoazoles **124** [75]. It was stated that the presence of electron-donating substituents in position 2 of the triazolo[1,5-*a*]pyrimidine molecule, and simultaneously the existence of powerful electron-withdrawing substituents in the *para*-position of the amine, leading to a decrease of the nucleophilic properties of the same, resulted in deactivation of the reacting compounds and thus lowering the yield of the obtained enamine (Scheme 45).

Scheme 45



R^1 = H, Me, CF_3, COOEt, NH_2
R^2 = Ph, C_6H_4-Me-p, C_6H_4-OMe-p, C_6H_4-Br-p

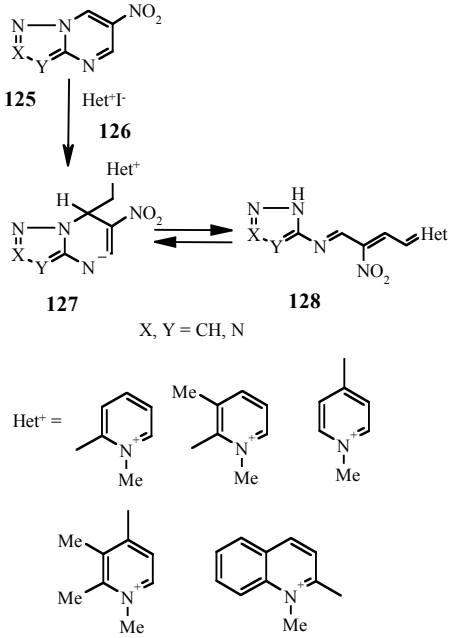
The cited publication presents two possible transformation pathways (Scheme 46) that differ in the site of the dissociation in the pyrimidine ring: C_7-N (pathway A) and N_4-C_5 (pathway B). An unusual transformation of condensed 5-nitropyrimidines is described in publication [76]. Bicyclic pyrazolo-, triazolo- and tetrazolo[1,5-*a*]-pyrimidines **125** are shown to react with various α– and γ–methylpyridinium iodides **126** either in the presence of an alkaline medium or in the presence of triethylamine. Electrically uncharged α– and γ–methylpyridines do not react with bicyclic compounds **125** unless activated. However, refluxing of the starting compounds **125** with methylpyridine tertiary ammonium salts **126** resulted in the formation of zwitterion adducts **127** with a potential of reversible cleavage of the C_7-N bond of the pyrimidine ring. According to the NMR data, the percentage of the open-chain form of the compound **128** in tautomeric mixture increases in the following series of annulation products: pyrazolo- < triazolo- < tetrazolo-adduct.

4.2. Reactions leading to the formation of five-membered rings.

An overwhelming majority of publications discussing transformations of 5-nitropyrimidines due to nucleophilic reactants consider their interaction with hydrazine or its derivatives. The interaction results in decomposition of pyrimidine ring followed by re-cyclization to form a pyrazole. This mode of interaction makes it possible to obtain various polysubstituted 4-nitropyrazoles.

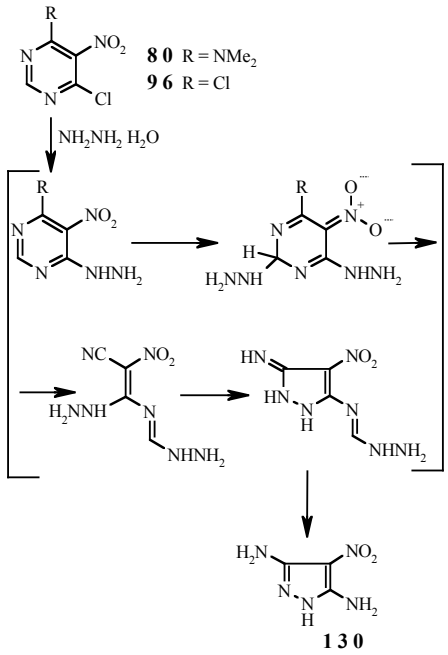
A classical example of the above re-cyclization of pyrimidines **80**, **96** to form pyrazole **130** under the action of hydrazine is a reaction reported in [77]. The reaction mechanism involves a hydrazine nucleophilic attack of position 2 in pyrimidine ring followed by cleavage of C_2-N_3 bond and ring opening with the formation of a cyano group. The next step is intramolecular cyclization involving both cyano and enehydrazine groups leading to the formation of pyrazole ring (Scheme 47).

Scheme 46



X, Y = CH, N

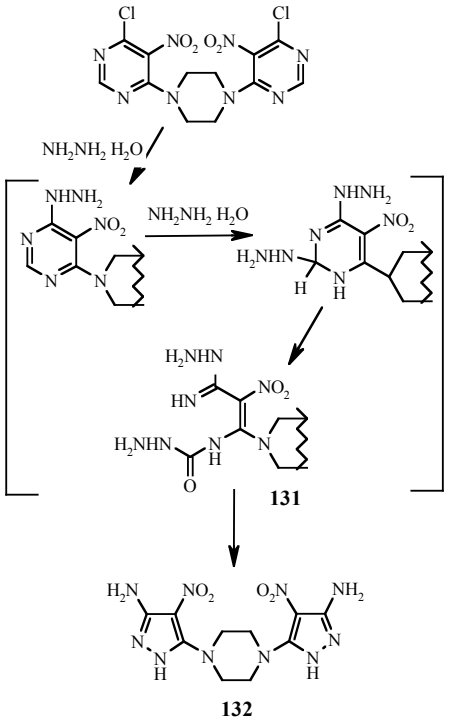
Scheme 47



The yield of the resulting pyrazole was shown to depend upon the nature of the amine substituent in position 4 of the pyrimidine. The highest yields were obtained when R = NMe_2, while reaction of 4-butylaminopyrimidine failed to give a pyrazole due to the formation of a stable 6-hydrazine derivative of the pyrimidine. This is probably caused by the fact that a bulky butylamine substituent forces nitro group out of the ring plane thus impairing the conjugation. The authors also suppose that electron-withdrawing conjugation effect (+M-effect) of the nitro group becomes considerably weaker and hydrazine attack upon the second site is hindered.

A somewhat different mechanism is described by the authors of [78], who suppose that re-cyclization does not involve formation of cyano derivative and, on the contrary, the key step of the process is an intramolecular transamination of enamine **131** followed by elimination of semicarbazide (Scheme 48). The yield of the target bis-pyrazole derivative **132** was about 30%.

Scheme 48



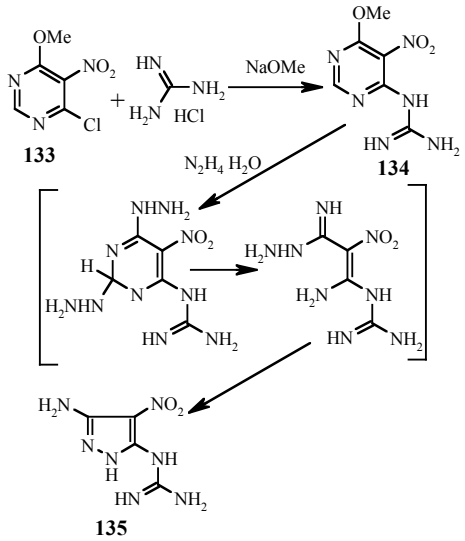
131

132

Authors of the publication [79] showed that 4-nitropyrazole derivative **135** containing guanidine substituent can release nitric oxide [80] under both oxidative and reducing conditions.

Preparation of such compounds is based on the reaction of 4-methoxy-5-nitro-6-chloropyrimidine **133** with guanidine followed by interaction of compound **134** with hydrazine hydrate. The investigators suggest the mechanism of the process presented on Scheme 49.

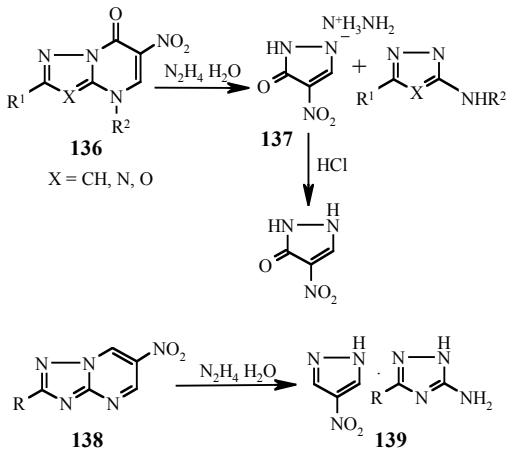
Scheme 49



133 **134** **135**

Unusual transformations (Scheme 50) of annulated 5-nitropyrimidines **136** were shown in [81].

Scheme 50



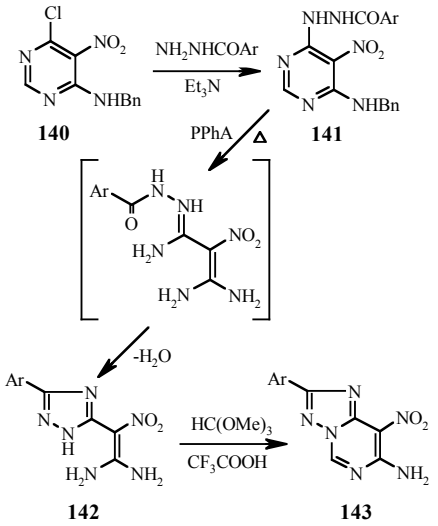
136 **137** **138** **139**

Heating of 4,7-dihydro-6-nitro-7-oxooxazolo[1,5-*a*]pyrimidines with hydrazine hydrate causes a contraction of pyrimidine cycle to occur. The nucleophilic attack of hydrazine takes place at position 5 of the azolopyrimidine resulting in cleavage of N_4-C_5 bond followed by the cleavage of the C_7-N_8 bond. Interaction of nitroazolo-pyrimidines **138** with hydrazine hydrate proceeds in a similar way and leads to the formation of 4-nitropyrazole – 5-aminoazole complexes **139**. The structure of the complexes was determined by the X-ray diffraction analysis. When heated in aqueous media the complexes dissociate with the formation of 4-nitropyrazole.

In contrast to reactions with hydrazine, interaction between 4-chloro-5-nitropyrimidines **140** and hydrazides

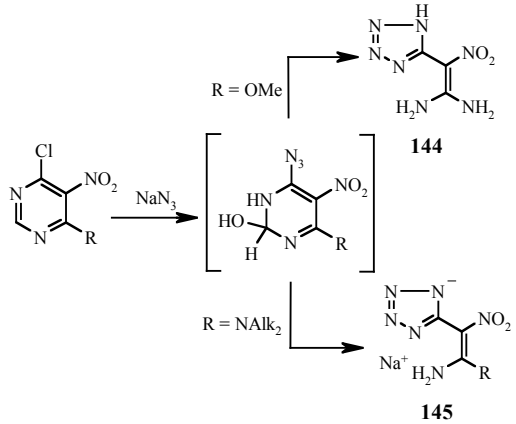
proceeds differently [82] and results in formation of 1,2,4-triazoles (Scheme 51). This can be explained by a possible attack of carbonyl carbon by the formed amino group. The interaction proceeds *via* formation of a corresponding pyrimidine derivative **141** followed by subsequent cleavage of the ring when the compound is heated in polyphosphoric acid. Treatment of the obtained enamine **142** with orthoformic ester in trifluoroacetic acid was found to lead to a closure of pyrimidine ring and formation of bicyclic [1,2,4]triazolo[1,5-*c*]pyrimidine **143**.

Scheme 51



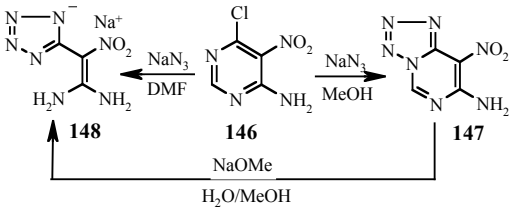
A number of publications discuss interaction between 4-chloro-5-nitropyrimidines with sodium azide. As expected (Scheme 52), the reaction does not terminate at the point of nucleophilic substitution of chlorine by azide group, but proceeds further and *via* formation of tetrazole cycle and cleavage of the C_2-N_3 bond of pyrimidine ring which terminates by formation of the corresponding β-tetrazolylenamines **144** and **145** [83].

Scheme 52



The same study showed that if a primary amino group is present in a pyrimidine molecule, a bicyclic tetrazolo-[1,5-*c*]pyrimidine **147** is formed which, when refluxed in alkaline media, undergoes pyrimidine ring opening and turns into sodium salt **148** (Scheme 53). The latter can also be obtained *via* direct treatment of 4-chloro-5-nitro-6-aminopyrimidine **146** with sodium azide in DMF.

Scheme 53



A similar transformation was accomplished in [84]. The authors obtained a target tetrazole **148** with 73% yield and identified its spatial structure by means of X-ray diffraction analysis (Figure 2). It was found out that hydrogen atom of tetrazole ring forms a hydrogen bond with oxygen of nitro group.

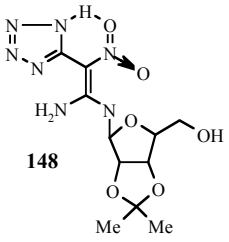
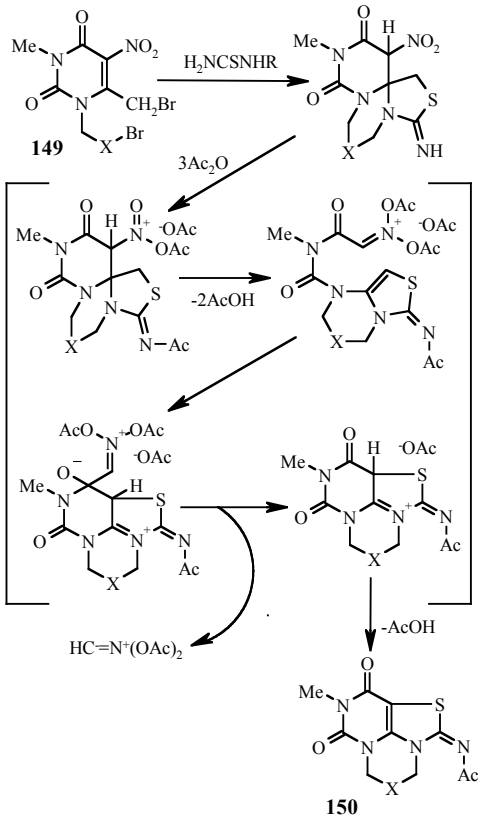


Figure 2

One-step preparation of new tricyclic compounds **150** containing a thiazole ring involved interaction between 5-nitropyrimidine dibromo derivatives **149** and thioureas was proposed by authors [85] according to Scheme 54. The authors of the publication assume that the following mechanism should comprise a step with the C_4-C_5 bond cleavage and simultaneous opening of the pyrimidine ring.

Scheme 54

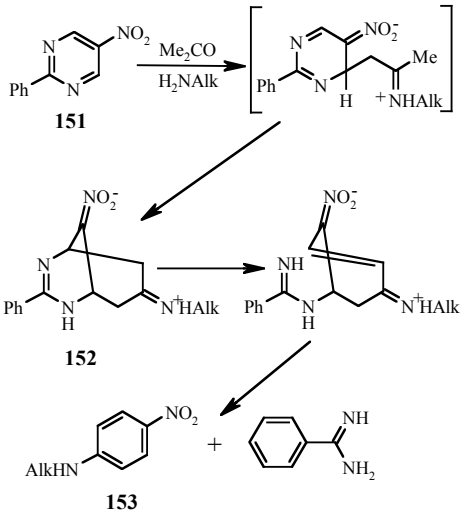


4.3. Reactions leading to formation of six-membered rings

This chapter presents some examples of re-cyclization of 5-nitropyrimidine to form various six-membered rings, *viz.*: benzene, pyridine, pyrimidine, and triazine. It is to be noted that most publications are devoted to re-cyclizations of 5-nitropyrimidines into pyridine and/or differently substituted pyrimidine rings.

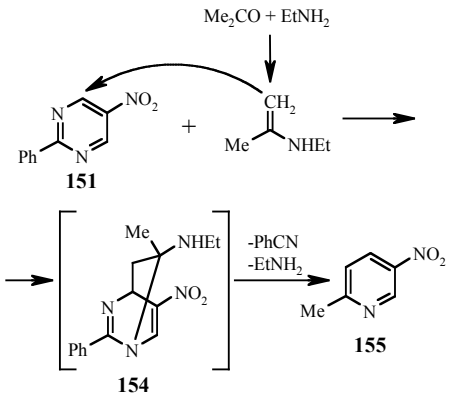
It is known [86] that treatment of 5-nitropyrimidine derivatives with acetone in the presence of strong bases results in formation of anion σ-complexes. According to [87], such σ-complexes can be formed during re-cyclization of pyrimidine ring into benzene (Scheme 55). It is possible that the first step consists in condensation of the starting compound **151** with enamine formed during condensation of ketone and primary amine. The proposed re-cyclization mechanism can be proven by the known fact that reactions of 3-nitrobenzene and dinitropyridine derivatives with ketones result in formation of bicyclic adducts, similar to adduct **152**. The authors, however, acknowledged that they failed to obtain any direct evidence of the intermediate **152** existence. The reaction seems to conclude with aromatization of the benzene ring *via* elimination of benzamidine and formation of nitroanilines **153** with the yield of about 30%.

Scheme 55



A study of the products obtained during the interaction of the starting compound **151** with ethylamine and acetone resulted not only in the isolation of the major product - nitroaniline **153**, but also 2-methyl-5-nitro-pyridine **155** (4% yield). The authors of [87] consider the starting nitropyrimidine to be susceptible not only to a nucleophilic attack, but also to Diels-Alder cycloaddition with reversed electron requirements (Scheme 56). The bicyclic adduct **154** eliminated benzonitrile and ethyl-amine and turned into 5-nitropyridine.

Scheme 56

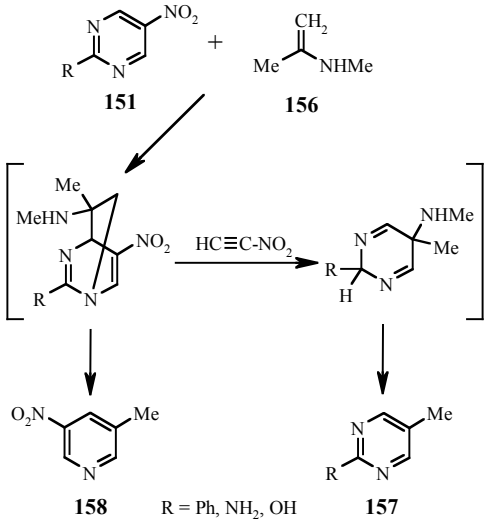


Thus, it was shown that reaction of pyrimidine nitro derivatives with aliphatic amines and acetone can involve either the three acetone carbon atoms (C-C-C), or two of

them (C-C) and result in the corresponding derivatives of benzene and pyridine.

Transformation of 5-nitropyrimidine **151** and its analogues disclosed in work [88] seems to proceed along the other route (Scheme 57). The main reaction products are shown to be 2-substituted 5-methylpyrimidines **157**. The reaction mixture also contained a small amount of 3-methyl-5-nitropyrimidine **158**.

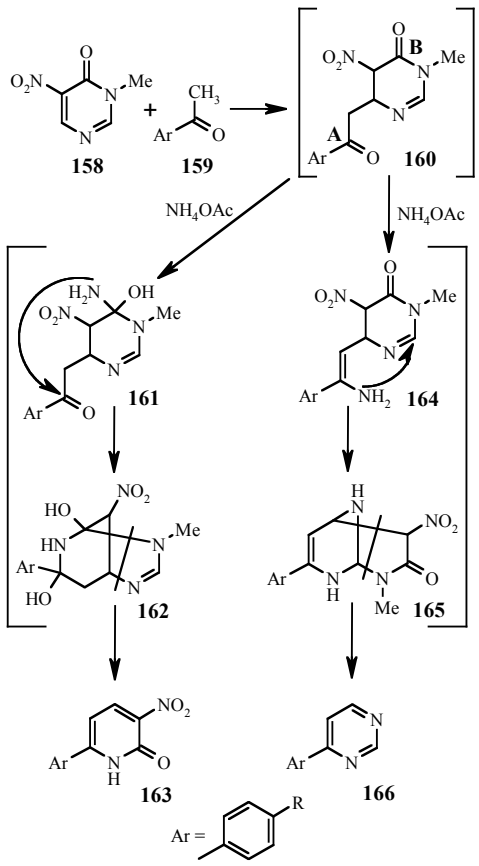
Scheme 57



The authors assume [88] that presence of a great amount of the tautomeric enamine form of N-methyl-acetonimine **156** under the conditions employed means that an electron-excessive dienophilic reactant interacts with the electron-deficient azadiene system of 5-nitro-pyrimidines in the manner of Diels-Alder synthesis with reversed electron requirements.

Interaction between pyrimidinone **158** and aceto-phenones in the presence of ammonium acetate in methanol was studied in [89] (Scheme 58). The ratio of resulting pyridines **163** to pyrimidines **164** was shown to depend upon electron properties of substituent attached to position 4 of acetophenone **159** (enol form) (Table 1). Electron-donating substituents, such as 4-NH_2, 4-NHAc, 4-OMe, 4-Me promote mostly the formation of pyridone **163**. If an electron-withdrawing substituent is present in position 4 of the acetophenone, the reaction changes its pathway and the main product is pyrimidine **166**. The authors of [89] consider the first step of the reaction to be an attachment of the enol form of the ketone to position 6 of the pyrimidinone.

Scheme 58



Adduct **160** is probably the common intermediate in the reaction. If the benzene ring of the acetophenone contains electron-withdrawing substituents, electrophilic properties of the carbonyl group increase considerably. This causes ammonia to attack the carbon (**A**) of the carbonyl group and leads to formation of the enamine **164**. Then the amino group attacks the least sterically hindered position 2 of the same molecule giving rise to a bicyclic intermediate **165**, which eliminates nitroacetamide and forms pyrimidine **166**. Acetophenones with electron-donating substituents in their benzene ring undergo amination of the carbonyl group **B**. The amino group of the resulting carbinolamine intermediate **161** attacks carbonyl **A** to form a bicyclic intermediate **162** that further transforms into pyridone **163**. The above considerations can be supported to some extent by the data represented in Table 1. However, in some cases the quantitative results cannot support the conclusion. For example, while the electron-donating effect of the methoxyl group exceeds that of methyl group, the ratio pyridone : pyrimidine is almost the same for both substituents.

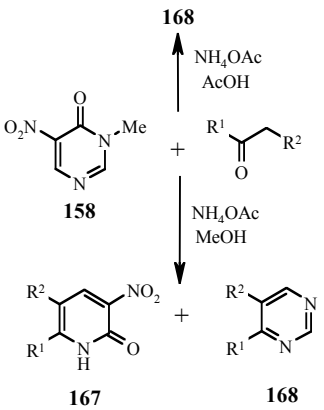
Table 1

Ratio pyridone:pyrimidine

R	Ratio **163** : **166**	R	Ratio **163** : **166**
H	51 : 49	Me	75 : 25
NH_2	99 : 1	Cl	53 : 47
AcNH	90 : 10	NO_2	23 : 77
MeO	76 : 24		

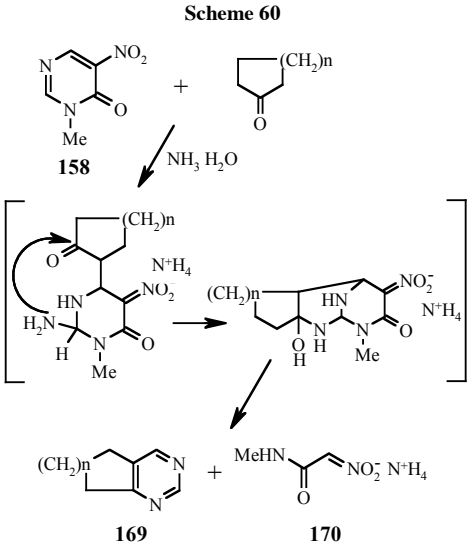
The mechanisms of pyrimidinone transformation into pyrimidine and pyridone are also discussed in [90]. Using the same 5-nitropyrimidinone **158** in reaction with aldehydes under conditions similar to those above, the researchers succeeded in obtaining 3-alkylsubstituted pyridones **167** (Scheme 59). Interaction with ethyl propyl ketone gave a mixture of 6-methyl-3-nitro-5-ethyl-2-pyridone (34%) and 4-methyl-5-ethylpyrimidine (17%). Application of cyclic ketones showed an interesting correlation between formation of the products **167** and **168** and the number of atoms in the ketone ring. Thus, cyclopentanone and cyclohexanone gave rise exclusively to corresponding bicyclic pyrimidines **168**, while cycloheptanone afforded only a 11% yield of pyrimidine **168** and 79% of the corresponding pyridone **167**. However, other investigators [89] reported that the use of acetic acid instead of methanol to dissolve the reactants resulted in the formation of pyrimidine **168** in a 90% yield, while formation of pyridone **167** was not observed. The authors of [91] explained it as follows: acetic acid forms strong intermolecular hydrogen bonds with oxygen atom attached to position 4 of pyrimidinone **168** which makes the attack on the C_4 carbon by amine impossible.

Scheme 59



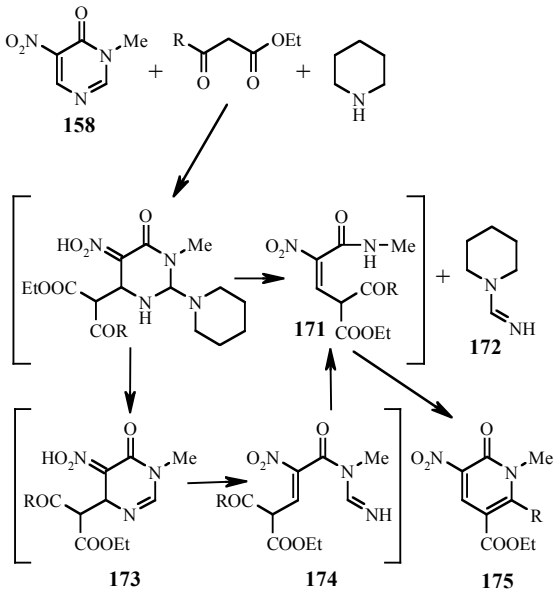
Reaction in ammonia aqueous solution proceeded in a similar way [92] due to the formation of strong hydrogen bonds with oxygen in pyrimidinone **158** (Scheme 60). The only product was a corresponding pyrimidine derivative **169** obtained with high yield. The authors also succeeded in isolation and identification of N-methylnitroacetamide ammonium salt **170** that supported the proposed reaction mechanism.

Scheme 60



Further, the authors of [92] undertook a thorough study of interactions between 5-nitropyrimidines and those ketones, which show properties of strong CH-acids and thus contain rather high amounts of enol forms. First, a reaction between 5-nitro-4-pyrimidinone **158** and phenyl or acetoacetic ester in the presence of piperidine was studied [93]. The authors suggested two mechanisms of formation of pyridone **175**. The process is supposed to involve enol attack on position 6 and piperidine attack on position 2 of the pyrimidine. Subsequent ring opening results in a polyfunctional alkene **171**. Formation of pyridone **175** results from an intra-

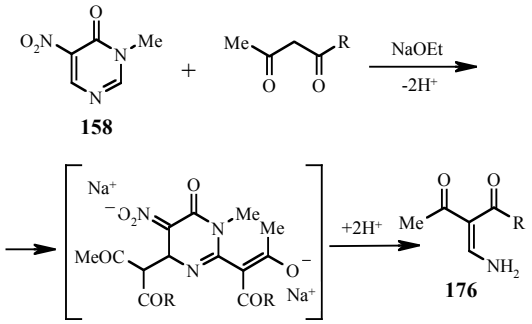
Scheme 61



molecular attack of carbamoyl nitrogen upon the acyl moiety. Another possible way is ring opening in intermediate **173** formed following addition to the starting pyrimidinone. Subsequent piperidine transamination of amidine fragment in compound **174** leads to the final pyridone **175**. The investigators identified formation of pentamethyleneformamidine **172** during this transformation that confirms the proposed mechanism (Scheme 61).

The authors of [94] used a stronger basic reactant, sodium ethoxide, instead of piperidine an attempt to conduct a similar reaction using acetylacetone or benzoylacetone (Scheme 62). However, the only isolated product obtained from the reaction of 5-nitropyrimidinone **158** was enamine **176**. NMR data showed that the moiety containing nitro group was completely destroyed under the reaction conditions. It should be noted that employing acetoacetic ester gave 70% yield of enamine **176**, while acetylacetone or benzoylacetone gave only a 40% yield of the product.

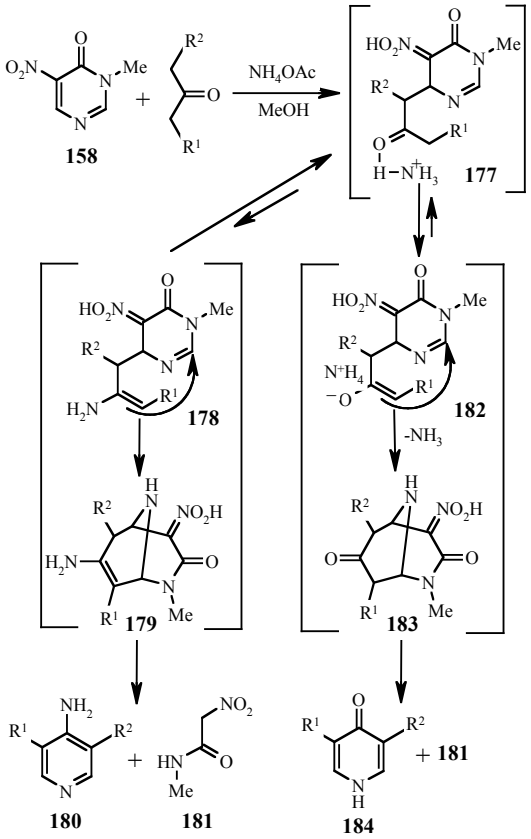
Scheme 62



R = OEt, Me, Ph

The above discussion shows that the composition of the products of interaction between pyrimidinone **158** and active methylene compounds is significantly influenced by the properties of the basic agent. In fact, publication [95] discloses that besides formation of the above pyridone **175** and enamine **176**, it is possible to obtain 4-aminopyridine **180** and pyridone **184** *via* transformation of compound **158** (Scheme 63). Thus, the use of such β-dicarbonyl compounds as acetoacetic esters (R^1=H, R^2=OMe, OEt, OPr, OC_5H_{11}) made it possible to obtain high yields of the corresponding 4-aminopyridines **180** and N-methylnitroacetamides **181**. The use of propyl and amyl esters also gave rise to the formation of 4-pyridone **184** with the yield lower than 12%. Later this reaction was extended to include other active methylene compounds containing following substituents: R^1=Me or OMe, R^2=OMe; R^1=H, R^2=Cl or NH_2. In every case there were obtained almost quantitative yields of 4-aminopyridines **180**. Triketo derivatives (R^1=R^2=COMe, R^1=R^2=COOEt) failed to give the trisubstituted aminopyridine **180**. This reaction resulted exclusively in the formation of 4-pyridone **184**.

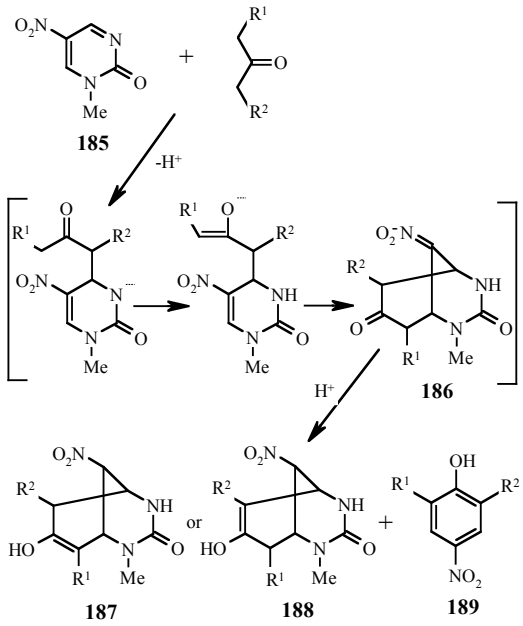
Scheme 63



The authors assume that the reaction begins with a nucleophilic addition of the diketone enol form to the electron-deficient position 6 of nitropyrimidinone **158**. The ketone group in adduct **177** is aminated with ammonium salt to form enamine **178**. Subsequent intramolecular cyclization gives rise to the bicyclic intermediate **179**, which eliminates nitroacetamide **181** and forms aminopyridine **180**. When triketones (R^1=R^2=COMe, R^1=R^2=COOEt) were used, enolization of the intermediate **177** proceeded faster than its transformation into enamine. Thus, 4-pyridone **184** is obtained *via* transformation of the enol form of compound **182** involving formation of a bicyclic intermediate **183**. Employing diketones with R^1=H, R^2=OPr, or OC_5H_{11} gives a mixture of 4-aminopyridine **180** and pyridone **184**. This can be explained by steric hindrance shielding the carbonyl group from the attack of ammonium salt. In a continuation of the investigation [94] triethylamine was found to be a convenient preparative basic agent. Its use resulted in an almost quantitative yield of the target 4-aminopyrimidine **180**.

The same reaction sequence was repeated [95] using 1-methyl-5-nitro-2-pyrimidinone **185** (Scheme 64), which is isomeric with the above 4-pyrimidinone **158**. The reaction mixture obtained was found to contain diazabicyclononenes **187** and **188**, that were isolated and identified. It was shown [96] that the pathway of this reaction is also significantly influenced by the nature of the basic reactant used. Thus, product **187** is formed, if the reaction is conducted in ethanol with addition of triethylamine, or in pyridine containing sodium ethoxide.

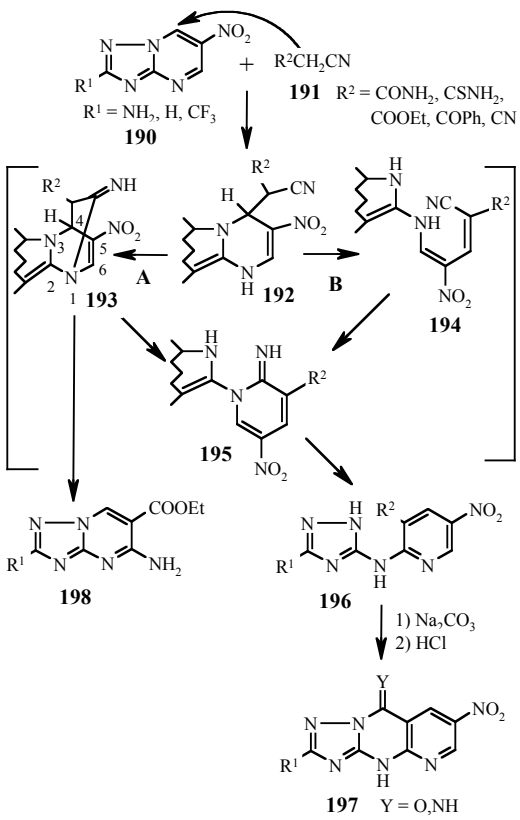
Scheme 64



Employing acetoacetic ester (R^1=H, R^2=COOEt) in dimethylformamide with addition of sodium ethoxide resulted in the formation of the bicyclic compound **188**, where the localization of double bond differs from that in compound **187**. Formation of a small amount of phenol **189** (R^1=R^2=COMe) was observed when the reaction was conducted in pyridine containing sodium ethoxide.

The above transformation of 5-nitropyrimidines into pyridines was used [97, 98] in the course of studying the possible re-cyclizations of pyrimidine ring in to bicyclic [1,2,4]triazolo[1,5-*a*]pyrimidines **190** (Scheme 65). For this purpose the researchers chose various acetonitrile derivatives as active methylene compounds. It was observed that, when triazolopyrimidines **190** interacted with cyano derivatives **191** in the presence of potassium carbonate in alcohol, they were transformed into triazolo[1,5-*a*]pyrimido[2,3-*d*]pyridines **197**. The experimental results and reported data allowed the authors to propose the following reaction mechanism.

Scheme 65

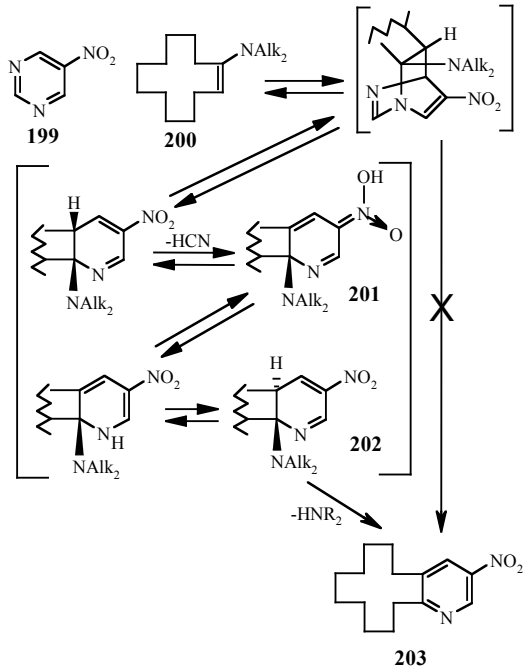


First, a nucleophilic attack on position 7 of triazolopyrimidine **190** results on formation of adduct **192**, which can turn either into a cyclic intermediate **193** (pathway **A**) or into an open-chain intermediate **194** (pathway **B**). Both intermediates then can undergo a rearrangement into iminonitropyrimidine **195**. It is to be noted that formation of acyclic intermediate was proposed for transformations of monocyclic nitropyrimidines with dinucleophilic reactants [99, 100]. Intermediate **195** undergoes Dimroth rearrangement to form 3-nitropyridine **196**. At the same time the formation of compound **195** from intermediate **193** as a result of the cleavage of the N_3-C_4 bond of the latter is also possible. Formation of 5-amino-6-carboethoxytriazolo[1,5-*a*]pyrimidine **198** may include the cyclic intermediate **193** eliminating C_5-C_6 moiety and resulting in the formation of nitroacetylene. Identification of compound **198** in the reaction mixture strongly suggests that the reaction proceeds *via* the pathway **A**.

The possibility of 5-nitropyrimidine **199** transformation into substituted nitropyrimidine under the action of enamine is described in a short publication [101]. The authors chose an unusual macrocyclic enamine **200** including a cyclodecene core (Scheme 66). Mechanism of the above transformation was discussed in detail in van der Plas's work [102]. Elimination of morpholine from

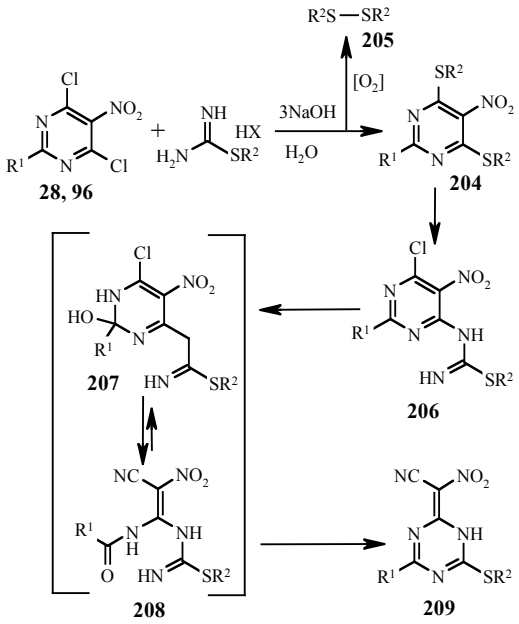
intermediate **201** was shown to be impossible, since it contains an amine moiety and an *ortho*-proton in S-*syn*-orientation. Obtaining the resulting pyridine derivative **203** in this reaction can be explained by series of tautomeric transformations of the molecule, possibly due to the presemce of a nitro group. The mechanism of the process is shown in Scheme 66. Intermediate **202**, on the contrary, contains a proton and morpholine in S-*anti*-orientation that facilitates an elimination of the secondary amine from the molecule.

Scheme 66



An unusual transformation of 6-chloro-5-nitropyrimidines **28**, **96** into 1,3,5-triazines by isothioureas in a strongly alkaline medium was investigated by authors of [103]. The whole process is outlined in the Scheme 67. The first step is obviously the formation of free base of S-alkyl(arylalkyl)isothiourea, which can either undergo a decomposition to form thiolate ions, or enter a nucleophilic substitution reaction to replace chlorine atoms of the pyrimidine ring. The first possible route results in the formation of 4,6-diarylalkyl(arylalkyl)thio-5-nitropyrimidines **204**. As the reaction mixture contains an excess of thiolate ions, exposing the mixture to air for a prolonged time can afford the corresponding disulfides **205**. The second possible pathway of the process results in formation of 4-chloro-5-nitro-6-(S-alkyl /arylalkyl /isothioureido)pyrimidines **206**, which sometimes can be isolated from the reaction mixture. Subsequently these compounds undergo a covalent hydration of the C_2-N_3 bond of pyrimidine ring with the formation of the covalent hydrate **207**, which undergoes a transformation into an open-chain form **208**. The latter undergoes re-cyclization and elimination of water resulting in the formation of 1,3,5-triazine derivatives **209**. The product ratio is shown to depend upon the nature of substituents in position 2 of pyrimidine ring and substituents attached to sulfur atom of the isothiuronium salt. Thus, a 2-methyl or 2-mercapto group (R^1) facilitates formation of a stable compound **206**, which cannot be attacked in position 2 of pyrimidine ring due to steric hindrance. The use of isothiuronium salts bearing electron-withdrawing substituents (e.g. R^2 = p-NO_2Ph) gave dimercaptopyrimidine **204** as the main product.

Scheme 67



5. Conclusion

In summary, the information presented in this review clearly indicates that the use of 5-nitropyrimidines in synthesis of organic compounds represents various interesting and unusual approaches. Simplicity of preparation and a great diversity of the starting materials, as well as their high reactivity make them the prospective synthons for preparation of various organic compounds and especially, heterocyclic systems of great theoretical and practical interest.

Acknowledgement. We thank the Civilian and Research Development Fund (project RUB2-2704-MO-05) for support of this work.

REFERENCES

[1] Akselrod, G.N.; Beresovskii, V.M. *Russ. Chem. Rev.* **1970**, *39*, 627.

[2] Brown D. J. In *The Pyrimidines*, J.Willey & Sons, New York, **1962**, pp 138-156.

[3] Bimmer, M.; Langen, P.; Plaul, H. German Patent 221,736, 1981; *Chem. Abstr.* **1982**, *104*, 68880p.

[4] Ridd, J. H. *Z. Chem.* **1968**, *6*, 201.

[5] Ficher, H. P. German Patent 2,356,644, 1973; *Chem. Abstr.* **1974**, *82*, 27230e.

[6] Frissen, A. E.; Marcelis, A. T. M. *Tetrahedron* **1986**, *45*, 5151.

[7] Christensen, B. E.; Stahl, Q.; Lehmkuhl, F. *J. Org. Chem.* **1971**, *36*, 2462.

[8] Kleine-Natrop, H. E. *Acta Allerg.* **1966**, *21*, 319.

[9] Sedov, A.L.; Makarov, V.A.; Nemeryuk, M.P.; Safonova, T.S. Second Russian Conf. on Enamine Chemistry, Perm, **1991**, 17.

[10] Marcelis, A.T.; Van der Plas, H.S. *J. Org. Chem.* **1986**, *51*, 67.

[11] Ladd, L. D. US Patent 4,336,255, 1981; *Chem. Abstr.* **1982**, *97*, 98377d.

[12] Makarov, V. A.; Sedov, A. L.; Nemeryuk, M. P.; Safonova, T. S. *Chem. Pharm. J.* **1993**, *27*, 245.

[13] Granik, V.G.; Zhidkova, A.M.; Glushkov, R.G. *Russ. Chem. Rev.* **1977**, *46*, 361.

[14] Filla, S. A.; Mathes, B. M.; Johnson, K. W.; Phebus, L. A.; Cohen, M. L.; Nelson, D. L.; Zgombick, J. M.; Erickson, J. A.; Schenck, K. W.; Wainscott, D. B.; Branchek, T. A.; Schaus, J. M. *J. Med. Chem.* **2003**, *46*, 3060.

[15] Gibson, E. S.; Lesiak, K.; Watanabe, K. A.; Gudas, L.J.; Pankiewicz, K. W. *Nucleosides and Nucleotides* **1999**, *18*, 363.

[16] Liu, M.-C.; Luo, M.-Z.; Mozdziesz, D. E.; Sartorelli, A. C. *Synth. Commun.* **2002**, *32*, 3797.

[17] Taylor, E. C.; Young, W. B.; Ward C. C. *Tetrahedron Lett.* **1993**, *34*, 4595.

[18] Furneaux, R. H.; Tyler P. C. *J. Org. Chem.* **1999**, *64*, 8411.

[19] Taylor, E. C.; Young, W. B. *J. Org. Chem.* **1995**, *60*, 7947.

[20] Batcho, A. D.; Leimgruber, W. *Org. Syntheses* **1990**, *7*, 34.

[21] Batcho, A. D.; Leimgruber, W. US Patent 3,976,639, 1976; *Chem. Abstr.* **1977**, *86*, 29624p.

[22] Makarov, V. A.; Anisimova, O. S.; Granik, V. G., *Chem. Heterocycl. Comp.*, **1997**, *33*, 276.

[23] Tsupak, E.B.; Tkachenko, Yu.N.; Pozharskii, A.F. *Chem. Heterocycl. Comp.* **1994**, *30*, 1077.

[24] Grahner, B.; Winiwarter, S.; Lanzner, W.; Muller, C. E. *J. Med. Chem.* **1994**, *37*, 1526.

[25] Tkachenko, Yu. N.; Tsupak, E. B.; Pozharskii, A. F. *Chem. Heterocycl. Comp.* **2000**, *36*, 307.

[26] Evans, G. B.; Furneaux, R. H.; Hutchison, T. L.; Kezar, H. S.; Morris, P. E.; Schramm, V. L.; Tyler, P. C. *J. Org. Chem.* **2001**, *66*, 5723.

[27] Stefanachi, A.; Leonetti, F.; Cappa, A.; Carotti, A. *Tetrahedron Lett.* **2003**, *44*, 2121.

[28] Hicks, J. L. J. *Labelled Compd. Radiopharm.* **1995**, *36*, 1029.

[29] Otmar, M.; Masojídková, M.; Buděšínský, M.; Holý, A. *Tetrahedron* **1998**, *54*, 2931.

[30] Elliott, A. J.; Kotian, P. L.; Montgomery, J. A.; Walsh, D. A. *Tetrahedron Lett.* **1996**, *37*, 5829.

[31] Norman, M. H.; Chen, N.; Chen, Z.; Fotsch, C.; Hale, C.; Han, N.; Hurt, R.; Jenkins, T.; Kincaid, J.; Liu, L.; Lu, Y.; Moreno, O.; Santora, V. J.; Sonnenberg, J. D.; Karbon, W. *J. Med. Chem.* **2000**, *43*, 4288.

[32] Martin, A.; Butters, T. D.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1999**, *10*, 2343.

[33] Martin, A.; Butters, T. D.; Fieet, G. W. J. *Chem. Commun.* **1998**, 2119.

[34] Gala, D.; Di Benedetto, D. J.; Kugelman, M.; Mitchell, M. B. *Tetrahedron Lett.* **2003**, *44*, 2721.

[35] Cotterill, I. C.; Cox, P. B.; Drake, A. F.; Le Grand, D. M.; Hutchinson, E. J.; Latouche, R.; Pettman, R. B.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3071.

[36] Hammarstrom, L. G. J.; Smith, D. B.; Talamas, F. X.; Labadie, S. S.; Krauss, N. E. *Tetrahedron Lett.* **2002**, *43*, 8071.

[37] Hammarstrom, L. G. J.; Meyer, M. E.; Smith, D. B.; Talamas, F. X. *Tetrahedron Lett.* **2003**, *44*, 8361.

[38] Buckman, B. O.; Mohan, R.; Koovakkat, S.; Liang, A.; Trinh, L.; Morrissey, M. M. Bioorg. *Med. Chem. Lett.* **1998**, *8*, 2235.

[39] Makara, G. M.; Ewing, W.; Ma, Y.; Wintner, E. *J. Org. Chem.* **2001**, *66*, 5783.

[40] Simo, O.; Rybar, A.; Alfoldi, J. *Synthesis* **1995**, 837.

[41] McGill, J.; Rees, L.; Suckling, C. J.; Wood, H. C. S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1299.

[42] Cushman, M.; Mihalic, J. T.; Kis, K.; Bacher, A. *J. Org. Chem.* **1999**, *64*, 3838.

[43] Dunn, C.; Gibson, C. L.; Suckling, C. J. *Tetrahedron* **1996**, 52, 13017.

[44] Busque, F.; Hopkins, S. A.; Konopelski, J. P. *J. Org. Chem.* **2002**, *67*, 6097.

[45] Boyle, P. H.; Hughes, E. M.; Khattab, H. A. *J. Chem. Res. Miniprint* **1991**, *2*, 358.

[46] Inoue, S.; Okada, K.; Tanino, H.; Kakoi, H. *Tetrahedron* **1994**, *50*, 2753.

[47] Susvilo, I.; Brukstus, A.; Tumkevicius, S. *Syn. Lett.* **2003**, 1151.

[48] Rusinov, V.L.; Chupakhin, O.N. *In Nitroazines*, Nauka, Siberian Department, Novosibirsk, 1991, pp 237-238.

[49] Murashima, T.; Nishi, K.; Nakamoto, K.-I.; Kato, A.; Tamai, R.; Uno, H.; Ono, N. *Heterocycles* **2002**, *58*, 301.

[50] Ogawa, K.; Itaya, T.; Fujii, T. *Heterocycles* **1994**, *38*, 1225.

[51] Fujii, T.; Ogawa, K.; Itaya, T.; Date, T.; Inagaki, J.-I.; Nohara, F. *Chem. Pharm. Bull.* **1995**, *43*, 408.

[52] Ogawa, K.; Nishii, M.; Inagaki, J.; Nohara, F.; Saito, T.; Itaya, T.; Fujii, T. *Chem. Pharm. Bull.* **1991**, *40*, 343.

[53] Saladino, R.; Stasi, L.; Crestini, C.; Nicoletti, R.; Botta, M. *Tetrahedron* **1997**, *53*, 7045.

[54] Duffy, K. J.; Tennant, G. *J. Chem. Soc., Chem. Commun.* **1995**, 2457.

[55] Ziegler, E; Sterk, H. *Monatsh. Chem.* **1967**, *98*, 1104.

[56] Granik, V. G.; Kaminka, M. E.; Grigoriev, N. B.; Severina, I. S.; Kalinkina, M. A.; Makarov, V. A.; Levina, V. I. *Chem. Pharm. J.* **2002**, *36*, 523.

[57] Sako, M.; Oda, S.; Ohara, S.; Hirota, K.; Maki, Y. *J. Org. Chem.* **1998**, *63*, 6947.

[58] Youssif, S.; Yamamoto, H. *Phosphorus, Sulfur, Silicon and Relat. Elem.* **1998**, *118*, 301.

[59] Romanova, I.P.; Kalinin, V.V.; Nafikova, A.A.; Yahvarov, D.G.; Zverev, V.V.; Kovalenko, V.I.; Rusinov, V.L.; Plekhanov, P.V.; Charushin, V.N.; Sinyashin, O.G. *Russ. Chem. Bull.* **2003**, *52*, 173.

[60] Sako, M.; Takeda, Y.; Hirota, K.; Maki, Y. *Heterocycles* **1996**, *42*, 31.

[61] Heravi, M. M.; Bakherad, M.; Rahimizadeh, M.; Bakavoli, M.; Ghassemzadeh, M. *Heterocycl. Commun.* **2004**, *10*, 335.

[62] Clark, J.; Gelling, I.; Neath, G. J. *Chem. Soc., Chem. Commun.* **1967**, 859.

[63] Clark, J.; Gelling, I.; Southon, I. W.; Morton, M. S. *J. Chem. Soc. C* **1970**, 494.

[64] Clark, J.; Curphey, M.; Southon, I. W. *J. Chem. Soc., Perkin Trans 1* **1974**, 1611.

[65] Makarov, V. A.; Sedov, A. L.; Anisimova, O. S.; Granik, V. G. *Chem. Heterocycl. Comp.* **1996**, *32*, 699.

[66] Makarov, V. A.; Sedov, A. L.; Nemeryuk, M. P.; Solov'eva, N. P.; Anisimova, O. S.; Safonova, T. S. *Chem. Heterocycl. Comp.* **1995**, *31*, 180.

[67] Azev, Yu. A.; Gryazeva, O. V.; Golomolzin, B. V. *Chem. Heterocycl. Comp.* **2003**, *39*, 1478.

[68] Nishiwaki, N.; Tohda, Y.; Ariga, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1997.

[69] Klutchko, S.; Hodges, J. C.; Blankley, C. J.; Colbry, N. L. *J. Heterocycl. Chem.* **1991**, *28*, 97.

[70] Lampe, J. W.; Hanna, R. G.; Piscitelli, T. A.; Chou, Y.- L.; Erhardt, P. W.; Lumma, W. C.; Greenberg, S. S.; Ingebretsen, W. R.; Marshall, D. C.; Wiggins, J. *J. Med. Chem.* **1990**, *33*, 1688.

[71] Potvin, P. G.; Wong, M.-H. *J. Chem. Soc., Chem. Commun.* **1987**, 672.

[72] Tohda, Y.; Ariga, M.; Kawashima, T.; Matsumura, E. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 201.

[73] Boyle, P. H.; Daly, K. M.; Leurquin, F.; Robinson, J. K.; Scully, D. T. *Tetrahedron Lett.* **2001**, *42*, 1793.

[74] Ulomsky, E.N.; Voronin, V.V.; Rusinov, V.L.; Chupakhin, O.N. *Russ. Chem. Bull.* **2001**, *50*, 682.

[75] Rusinov, V.L.; Tumashov, A..A.; Pilicheva, T.L.; Chupakhin, O.N. *Russ. J. Org. Chem.* **1991**, *27*, 1100.

[76] Rusinov, G.L.; Plekhanov, P.V.; Rusinov, V.L.; Chupakhin, O.N.; Aleksandrov, G.G. *Russ. J. Org. Chem.* **1998**, *34*, 263.

[77] Guillard, J.; Goujon, F.; Badol, P.; Poullain, D. *Tetrahedron Lett.* **2003**, *44*, 5943.

[78] Makarov, V. A.; Sedov, A. L.; Nemeriuk, M. P.; Safonova T. S. *Chem. Heterocycl. Comp.* **1994**, 971.

[79] Makarov, V. A.; Danilov, A. V.; Levina, V. I.; Grigoriev, N. B.; Schmidtke, M.; Stelzner A.; Granik V. G. *Prob. Biol. Med. Pharm. Chem.* **2002**, 45.

[80] Granik, V.G.; Grigoriev, N.B. *Medicinal Chemistry*, Vuzovskaya Kniga, Moscow, 2004, pp. 360.

[81] Rusinov, V.L.; Myasnikov, A.V.; Chupakhin, O.N.; Aleksandrov, G.G. *Chem. Heterocycl. Comp.* **1991**, *27*, 530.

[82] Gatta, F.; Del Giudice, M. R.; Borioni, A.; Mustazza, C., Fazio, C. *J. Heterocycl. Chem.* **1994**, *31*, 1171.

[83] Makarov, V. A.; Sedov, A. L.; Nemeryuk, M. P.; Solovieva, N. P.; Safonova, T. S. *Chem. Heterocycl. Comp.* **1994**, *30*, 846.

[84] Babin, D.; Terrie, I.; Girardin, M.; Ugolini, A.; Demoute, J.-P. *Tetrahedron Lett.* **1994**, *35*, 103.

[85] Kinoshita, T.; Watanabe, Y.; Takaishi, Y.; Okunaka, T.; Nakao, S.; Furukawa, S. *Chem. Pharm. Bull.* **1993**, *41* 1485.

[86] Matsumura, E.; Tohda, Y.; Ariga, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2174.

[87] Gromov, S.P. *Russ. Chem. Bull.* **1994**, *43*, 1041.

[88] Yurovskaya, M. A., Ivanenkov, Y. A., Starkova, A. V. *Chem. Heterocycl. Comp.* **2002**, *38*, 1140.

[89] Nishiwaki, N.; Yamashita, K.; Azuma, M.; Adachi, T.; Tamura, M.; Ariga, M. *Synthesis* **2004**, 1996.

[90] Nishiwaki, N.; Wang, H.-P.; Matsuo, K.; Tohda, Y.; Ariga, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2261.

[91] Nishiwaki, N.; Adachi, T.; Matsuo, K.; Wang, H.-P.; Matsunaga, T.; Tohda, Y.; Ariga, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 27.

[92] Nishiwaki, N.; Matsunaga, T.; Tohda, Y.; Ariga, M. *Heterocycles* **1994**, *38*, 249.

[93] Nishiwaki, N.; Morimura, H.; Matsushima, K.; Tamura, M.; Ariga, M.A. *Heterocycles* **2003**, *61*, 19.

[94] Nishiwaki, N.; Matsushima, K.; Chatani, M.; Tamura, M.; Ariga, M. *Synlett* **2004**, 703.

[95] Nishiwaki, N.; Azuma, M.; Tamura, M.; Hori, K.; Tohda, Y.; Ariga, M. *Chem. Commun.* **2002**, 2170.

[96] Nishiwaki, N.; Tohda, Y.; Ariga, M. *Synthesis* **1997**, 1277.

[97] Rusinov, V.L.; Pilicheva, T.L.; Tumashov, A.A.; Egorova, L.G.; Chupakhin, O.N. *Chem. Heterocycl. Comp.* **1994**, *30*, 213.

[98] Chupakhin, O.N.; Rusinov, V.L.; Tumashov, A.A.; Pilicheva, T.L.; Sidorov, E.O.; Karpin, I.V. *Chem. Heterocycl. Comp.* **1991**, *27*, 210.

[99] Rose, F. L.; Brown, D. J. *J. Chem. Soc.* **1956**, 1953.

[100] Brown, D. J.; Harper, J. S. *J. Chem. Soc.* **1965**, 5542.

[101] Shkil, G. P.; Sagitullin, R. S. *Tetrahedron Lett.* **1994**, *35*, 2075.

[102] Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 2693.

[103] Sedov, A. L.; Nemeryuk, M. P.; Makarov, V. A.; Solov'eva, N. P.; Safonova, T. S. *Chem. Heterocycl. Comp.* **1991**, *27*, 804.