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Methods for the synthesis of aza(deaza)xanthines as a basis of biologically active compounds

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The review covers methods for the synthesis of aza(deaza)xanthines, *i.e.*, fused pyrrolo-, pyrazolo- and triazolopyrimidine heterocyclic systems, which are common core structures of various biologically active compounds. The extensive range of modern synthetic approaches is organized according to target structures and starting building blocks. The presented material is intended to benefit broad audience of specialists in the fields of organic, medicinal and pharmaceutical chemistry.
The bibliography includes 195 references.

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I. Introduction

Fused heterocyclic systems such as pyrrolo-, pyrazolo- and triazolopyrimidine-2,4-diones may be considered as analogues of xanthine (3,7-dihydropurine-2,6-dione). Although the first aza- and deazaxanthines were described as early as the 1950s,[1–4] the interest in these compounds is now revived. Intensive studies deal with the development of novel synthetic approaches to these compounds and with optimization of the known procedures, introduction of various substituents into pyrimidine and azole rings, transformation of a heterocycle ring, *etc*. Such interest is caused by a wide range of biological activities which have been found for these compounds. They are potent DNA-gyrase inhibitors and may be regarded as potential bactericidal agents.[5] Established also is a pronounced activity of these systems towards human thymidine phosphorylase, making them potential drugs for cancer therapy.[6–10] Moreover, representative compounds of this class possess high affinity for adenosine receptors and may be recommended as agents to treat asthma [11–13] and Parkinson's disease.[14–16] Aza-(deaza)xanthines show potent inhibitory activity to dipeptidyl peptidase-IV and act as potential antidiabetic drugs;[17] they exhibit considerable response for chronic pain and inflammation,[18] have an inhibitory action on purine nucleoside phosphorylase and are proposed as immunosuppressors to treat such diseases as rheumatoid arthritis.[19,20] Certain compounds of this series were found [21] to inhibit cyclic guanosine monophosphate phosphodiesterase (cGMP) and may be used as cardiovascular drugs. Pronounced inhibitory activity to phosphodiesterase 5 makes them potential second-generation drugs to treat erectile disfunction and pulmonary arterial hypertension,[22,23]

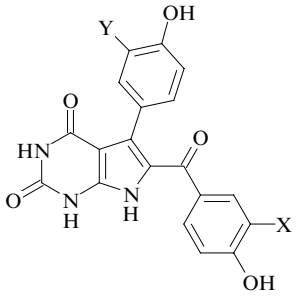
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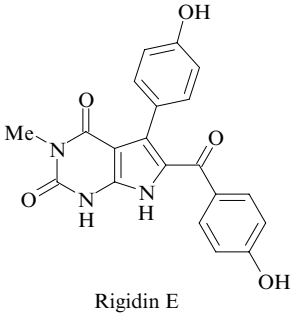
while their ability to inhibit coagulation factor Xa can serve for treatment of thromboembolic disorders.[24, 25] Certain derivatives of pyrazolopyrimidines show antifungal activity and may be used as herbicides in agriculture.[26]

Pyrrolo-, pyrazolo- and triazolopyrimidine-2,4-diones are encountered in nature. The heterocyclic system of xanthine forms the basis of known plant alkaloids caffeine, theophylline and theobromine. Moreover, recently an alkaloid rigidin A has been isolated from *Eudistoma* cf. *rigida*.[27] Later, its analogues, namely, rigidins B – E,[28] isolated from the same source, were identified. These compounds exhibited high cytotoxic activity towards a series of tumour cells.[29] Studies on the mechanism of their action showed that rigidins inhibit polymerization of tubuline in the HeLa cell culture.[30]

Structure of rigidins



Rigidin A: X = Y = H;
Rigidin B: X = OMe, Y = H;
Rigidin C: X = H, Y = OMe;
Rigidin D: X = Y = OMe



Rigidin E

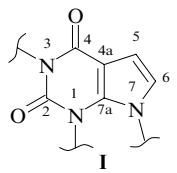
We are involved in the successful search for novel highly potent antiviral agents. In particular, compounds based on purine and pyrimidine heterocyclic systems were discovered, possessing high activity towards cytomegaloviruses, HIV-1 and Epstein – Barr viruses.[31 – 36] Therefore, we assume aza- and deazaxanthine to be very promising objects to continue the search for novel viral replication antagonists among them.

However, until recently, the general approaches to the above compounds were not adequately covered in the world scientific literature. By now, only numerous fragmentary data concerning this subject have been published.[37 – 39] In the present review an extensive literature material is classified according to the types of heterocyclic systems, methods of bond formation and reagents used, which should help the researches in choosing the synthetic methods for the preparation of novel biologically active derivatives of pyrrolo-, pyrazolo- and triazolopyrimidine-2,4-diones.

II. Pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones

The core of pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **I**, which are 7-deaza analogues of xanthine, comprises pyrimidine and pyrrole rings fused at the C=C bond. Most often, such systems are obtained through the annulation of a five-membered ring to a pyrimidine moiety; transformations yielding six-membered ring are applied more rarely.

Structure I



I

II.1. Closure of a pyrrole ring

Approaches to the formation of a pyrrole ring annulated to an azine moiety may be classified according to the type of the bonds formed (Fig. 1). The methods for the synthesis of the heterocyclic system **I** *via* a pyrrole ring closure are subdivided into 4 groups, depending on the bonds formed:

1) C(4a) – C(5) and C(6) – N(7) (method **IA**);
2) C(4a) – C(5) and N(7) – C(7a) (method **IB**);
3) C(5)=C(6) and N(7) – C(7a) (method **IC**);
4) C(6) – N(7) and N(7) – C(7a) (method **ID**).

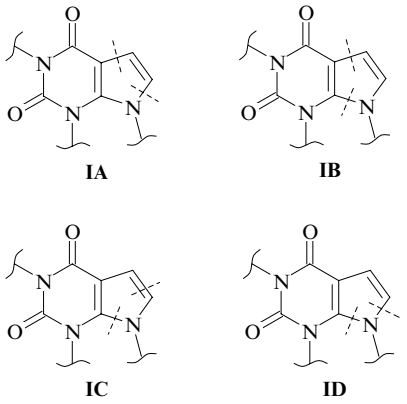


Figure 1. Types of formation of a five-membered ring in the synthesis of pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-diones **I** (here and below the dashed line designates the forming bonds).

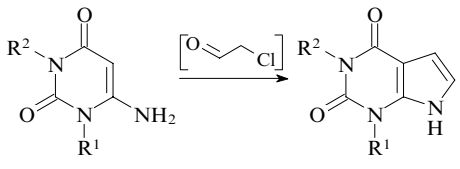
II.1.a. Method IA

The most commonly used approach to pyrrole ring closure is the formation of C(4a) – C(5) and C(6) – N(7) bonds, as in this case, commercially available 6-aminouracil (**1a**) and its derivatives are used as parent compounds. A large number of procedures are known for the synthesis of pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **2** having different substituents in the pyrimidine ring.

Noell and Robins[40] have obtained 1,3-dimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**2b**; $R^1 = R^2 =$ Me) by condensation of 6-amino-1,3-dimethyluracil (**1b**; $R^1 = R^2 =$ Me) with an excess of chloroacetaldehyde dimethyl acetal in the presence of aqueous HCl. However, the yield of the product in this case did not exceed 48%.

For pyrrole ring closure, chloroacetaldehyde may be used as a reagent. Senda and Hirota[41] have shown that 1,3-disubstituted 6-dimethyluracils **1** are condensed with an excess of chloroacetaldehyde in water in the presence of sodium acetate at 80 °C (Scheme 1).

Scheme 1



1 **2**

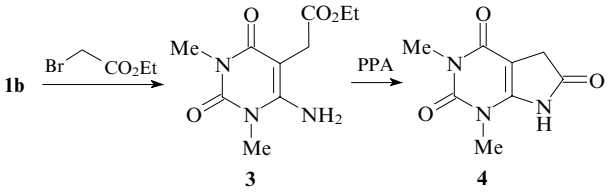
R^1, R^2 = H, Alk, Ar

This results in the corresponding 1,3-disubstituted pyrrole[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **2**, the yield depending on the nature of substituents and varying over a wide range from 11% (for the compounds with $R^1 = Bu^n$, $R^2 = H$) to 82% ($R^1 = Ph$, $R^2 = Me$). Chen *et al.*[42] have found that under the same conditions, unsubstituted 6-aminouracil (**1a**) afforded pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **2a** ($R^1 = R^2 = H$) in a yield of 98%.

However, when this reaction was employed to obtain nucleoside analogues,[43,44] the yield of the target compounds was less than 9%. The yields of the corresponding 1,3-dimethylpyrrole[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones upon condensation of 6-amino-1,3-dimethyluracil (**1b**) with bromoacetone, phenacyl bromide and *p*-bromophenacyl bromide were also moderate (10%–16%).[45]

Condensation of 6-amino-1,3-dimethyluracil (**1b**) with ethyl bromoacetate under mild conditions to give product **3** has been reported. In the presence of polyphosphoric acid (PPA) at 140–150 °C, compound **3** cyclized to give 1,3-dimethylpyrrolo[2,3-*d*]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4**). However, in this case, the yield of the target compound was also moderate (< 50%) (Scheme 2).[46]

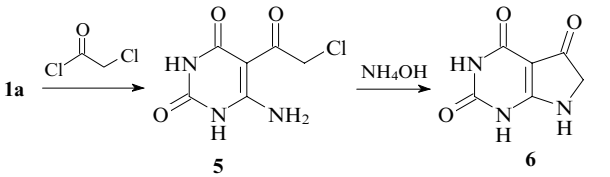
Scheme 2



3 **4**

Noell and Robins[40] used an equimolar amount of chloroacetyl chloride in reaction with 6-aminouracil (**1a**) in DMF, the process afforded 6-amino-5-chloroacetyluracil (**5**) in a quantitative yield. Refluxing this product in 28% aqueous ammonia for 5 h resulted in the closure of a pyrrole ring. The target pyrrolo[2,3-*d*]pyrimidine-2,4,5-(1*H*,3*H*,6*H*)-trione (**6**) was obtained in 57% yield (Scheme 3).

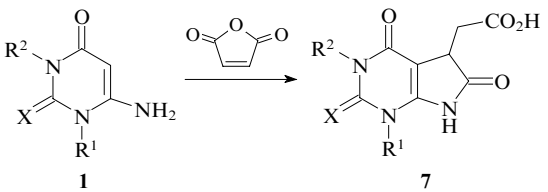
Scheme 3



5 **6**

A series of publications describes synthetic approaches to pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones based on the addition of 6-amino group of uracil derivatives to the activated double bond of alkenes followed by cyclization. Thus, Cobo *et al.*[46] refluxed 6-aminouracil and its 2-thio analogue with an excess of maleic anhydride in acetonitrile.

Scheme 4



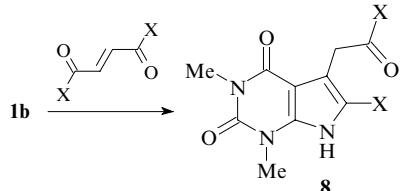
1 **7**

R^1, R^2 = H, Me; X = O, S

As a result, the corresponding (hexahydro-2,4,6-trioxopyrrolo[2,3-*d*]pyrimidine-5-yl)acetic acids and their thioxo analogues **7** were obtained, their yields being 67%–95% (Scheme 4). The substituents at the nitrogen atoms were shown to have almost no influence on the yield of the desired product.

Tamura *et al.*[47] performed the condensation of 6-amino-1,3-dimethyluracil (**1b**) with dibenzoyl- and diacetylethylenes. The reaction afforded pyrrolo[2,3-*d*]pyrimidine-2,4-diones **8** in 60% and 48% yields, respectively (Scheme 5).

Scheme 5



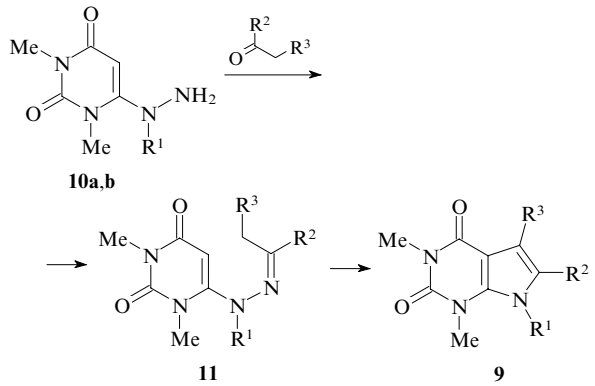
8

X = Me, Ph

The reactions involving 6-hydrazinouracil belong to the same type of a pyrrole ring closure. Thus, Senda and Hirota[48] described a method for synthesis of 5,6-disubstituted 1,3-dimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **9** (Scheme 6). Condensation of 6-hydrazino-1,3-dimethyluracils **10a**,**b** with various aldehydes and ketones was the key step of the transformation: upon heating in xylene or in the absence of solvent, hydrazones **11** were formed, yielding the desired pyrrolo[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-diones **9** on refluxing in ethylene glycol or tetraline. This was accompanied by evolution of ammonia.

Pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **9** were also obtained upon refluxing these reactants in ethylene glycol or tetralin without isolation of the intermediate hydrazides. Attempts to close the pyrrole ring under the catalysis by Lewis acids or concentrated mineral acids were unsuccessful. The authors gave no synthetic details.

Scheme 6



10a,**b** **11** **9**

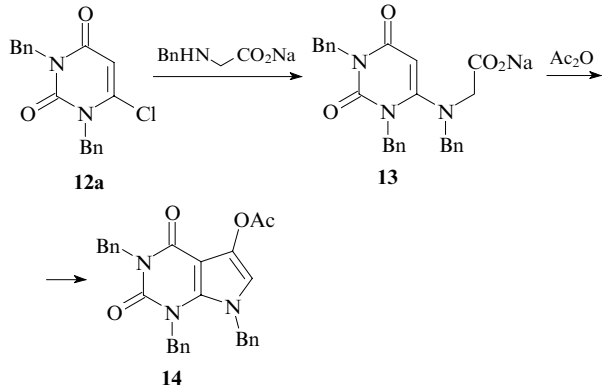
10: R^1 = H (**a**), Me (**b**); R^2, R^3 = H, Me, Ph; R^2–R^3 = $(CH_2)_4$

II.1.b. Method IB

In all methods of type **IB** for the synthesis of pyrrolo[2,3-*d*]-pyrimidine-2,4-diones described in the literature, 6-chlorouracil derivatives were used as the starting compounds. Condensation of such compounds with an amine component is followed by the cyclization to give a pyrrole moiety. Depending on the nature of the amine component, these syntheses may be subdivided into two groups, the first group using the derivatives of amino acids and the second

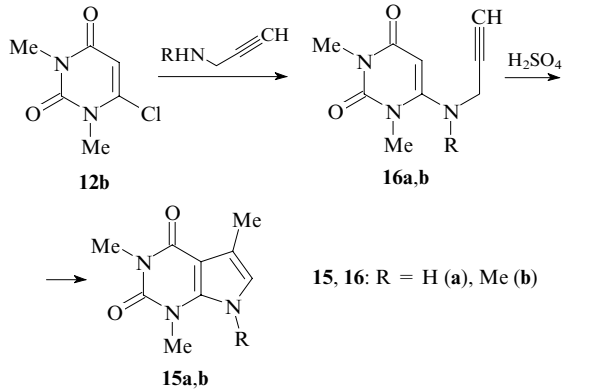
one using the derivatives of propargylamine. The condensation of 1,3-dibenzyl-6-chlorouracil (**12a**) with the sodium salt of N-substituted glycine affords 6-amino derivative **13**. Closure of the pyrrole ring occurs on treating compound **13** with acetic anhydride. As a result, 5-acetoxypyrrolo[2,3-*d*]-pyrimidine-2,4-dione **14** is obtained in a good yield (86.5%) (Scheme 7).[49]

Scheme 7



Kawahara *et al.*[50] described a synthetic procedure for the preparation of 5-methylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **15a**,**b** in which 1,3-dimethyl-6-chlorouracil (**12b**) was used as a starting compound. The latter was treated with an excess of propargylamine or *N*-methylpropargylamine to give the intermediate 1,3-dimethyl-6-propargylamino- or 1,3-dimethyl-6-(*N*-methyl-*N*-propargylamino)uracil (**16a**,**b**). The products obtained transformed into the corresponding 7-deazaxanthines **15a**,**b** in yields of 77.5% – 97% in the presence of concentrated sulfuric acid (Scheme 8).

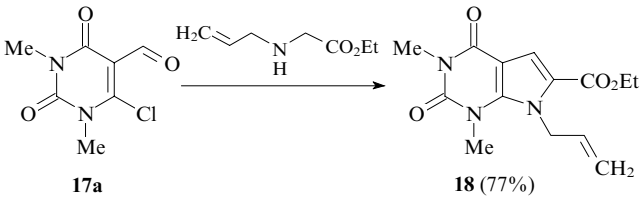
Scheme 8



II.1.c. Method IC

The reaction described by Muzychka *et al.*[51] should also be classified as the type **IC** closure of a pyrrole ring. Treating 6-chloro-5-formyluracil **17a** with the ethyl ester of *N*-allylglycine furnishes the 6-ethoxycarbonyl derivative of pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **18** in a good yield (Scheme 9).

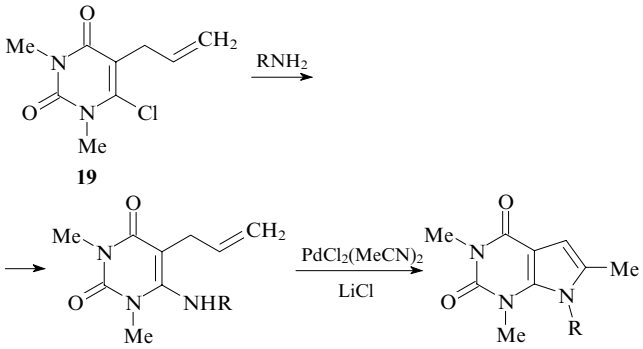
Scheme 9



II.1.d. Method ID

Ishikawa *et al.*[52] proposed a method of palladium-catalyzed pyrrole ring closure according to type **ID**. The starting 5-allyl-6-chloro-1,3-dimethyluracil (**19**), derived from 5-allylbarbituric acid, was treated with an excess of an amine to give 6-amino derivatives of uracil **20**. The cyclization was performed using a catalytic amount of $PdCl_2(MeCN)_2$ and an excess of LiCl. 7-Substituted 1,3,6-trimethylpyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **21** were obtained in low yields (Scheme 10).

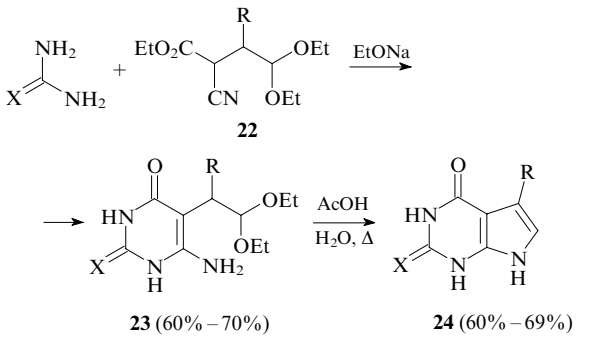
Scheme 10



R = H, Et, Pr^n, CH_2CH_2OH, Bn

The method originally described by Westphal and Stroh[53] and subsequently reproduced by Xie *et al.*[54] relates to the same type of pyrrole ring closure. It was shown that condensation of equimolar amounts of diethyl ketal **22** with urea or thiourea in the presence of sodium ethoxide in ethanol affords 6-amino-5-(2,2-diethoxyethyl)uracils **23** in good yields. Heating their solutions in 50% aqueous acetic acid gives the corresponding pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **24** and their thio analogues (Scheme 11).

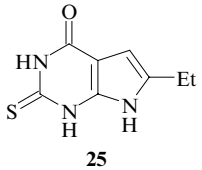
Scheme 11



R = H, Me; X = O, S

The same synthetic route was used to prepare 2-thio derivative of pyrrolo[2,3-*d*]pyrimidine **25** (90% yield),

Structure 25



which acts as DNA-gyrase inhibitor and is thus a potential bactericide.[5]

II.2. Closure of a pyrimidine ring

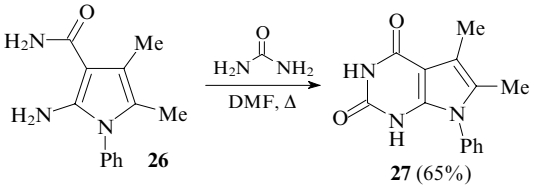
The reported methods of pyrimidine ring closure based on 2-aminopyrrol-3-carboxylic acid derivatives affording pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones may be subdivided into two groups according to the reagents in use:

1) fusing with urea or ethyl chloroformate;
2) condensation with alkyl or aryl isocyanates.

II.2.a. Reactions with urea or ethyl chloroformate

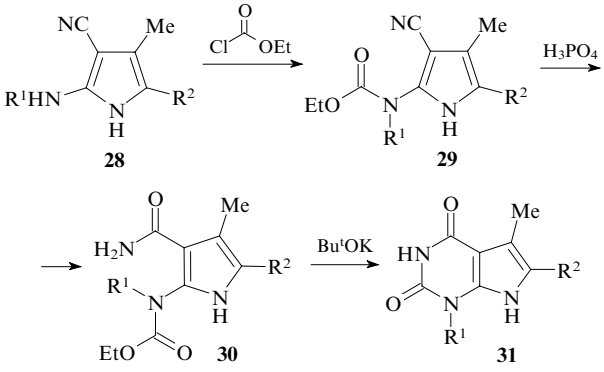
Eger *et al.*[55] obtained 5,6-dimethyl-7-phenylpyrrol[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)dione (**27**) by refluxing 2-amino-4,5-dimethyl-1-phenylpyrrole-3-carboxamide (**26**) with urea in DMF (Scheme 12).

Scheme 12



Ethyl chloroformate may be considered as an analogue of urea to be used as a source of the carbonyl moiety. Thus, Etson *et al.*[56] treated pyrrole-3-carbonitriles **28** with ethyl chloroformate to obtain the corresponding carbamates **29** (Scheme 13). In phosphoric acid solutions, the nitrile group in compounds **29** was transformed into the amide one, and the subsequent cyclization of products **30** under the action of potassium *tert*-butoxide or under reflux in octanol gave 5,6-disubstituted pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **31** in 69% – 99.5% yields.

Scheme 13



R^1 = H, Me; R^2 = Me, Et, Bu^i, Bn, $CH_2C_6H_4OH$-4, Ph

Oxalyl chloride (reaction in diglyme)[30, 57] and triphosgene[58] can also act as sources of the carbonyl moiety.

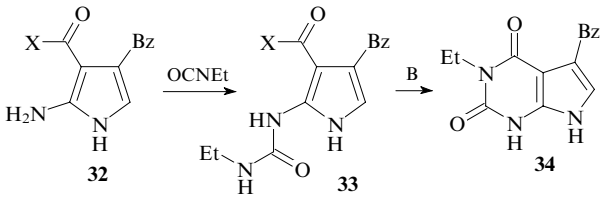
II.2.b. Condensation with alkyl or aryl isocyanates

Condensation of amides and ethyl 2-aminopyrrole-3-carboxylates **32** with isocyanate affords urea derivatives **33**, which cyclize in the presence of bases to give 3- and 5-substituted pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **34** (Scheme 14).[59]

3-Substituted 5,6-dihydropyrrole[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **35** were obtained in the same way.[60]

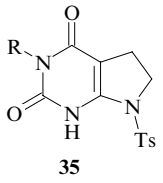
Pittala *et al.*[61] and Meyer *et al.*[62] modified the synthetic procedure as illustrated in Scheme 14. The compounds **36** resulting from condensation of 2-aminopyrrole-3-carboxylates with 2-chloroethyl isocyanate were first aminated with a secondary amine (Scheme 15) to afford the corresponding amine **37** and then the pyrimidine ring was closed.

Scheme 14



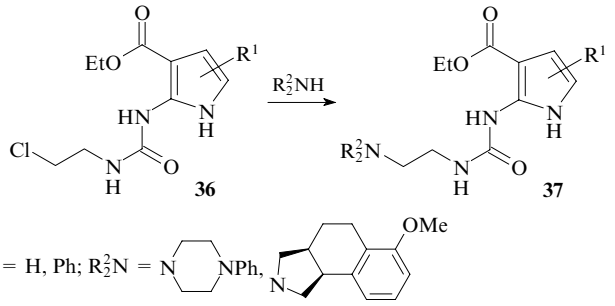
X = NH_2, OEt; B is base

Structures 35



R = Ph, Bn, CH_2OMe;
Ts is *p*-toluenesulfonyl

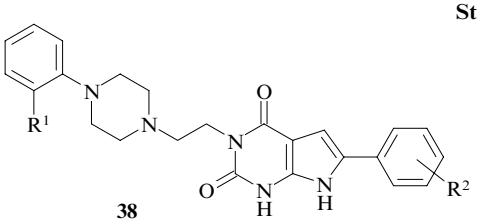
Scheme 15



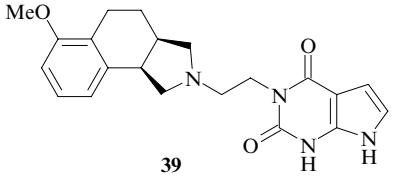
R^1 = H, Ph; R^2_2N =

This procedure gave rise to 3-substituted pyrrolo[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-diones **38** in yields of 85% – 98% in the last step and to compound **39** (23.8% yield in the last step).

Structures 38, 39



R^1 = OMe, Cl; R^2 = H, Me, OMe, Cl

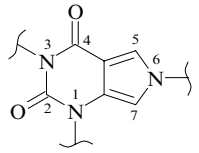


III. Pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones

Pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **II** in which the pyrrole ring is annulated *via* the single C(3) – C(4) bond to a

pyrimidine-2,4-dione moiety are the least known deaza analogues of xanthine.

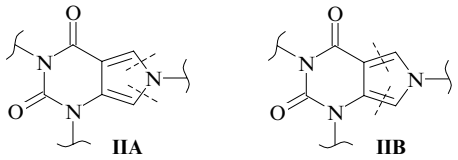
Structure II



II

III.1. Closure of a pyrrole ring

These heterocycles are usually prepared by closure of a pyrrole ring. Two groups of methods can be distinguished, resulting in the formation of the symmetrical C – N (method **IIA**) and C=C bonds (method **IIB**) (Fig. 2).



IIA **IIB**

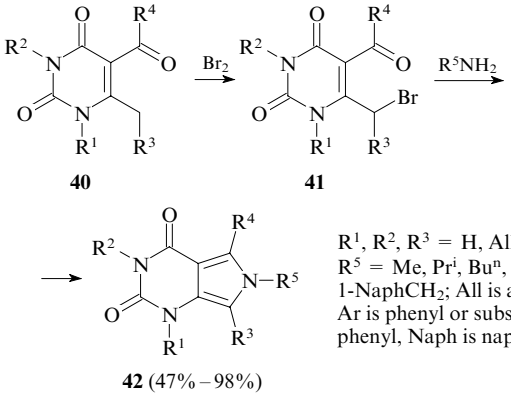
Figure 2. Types of formation of a five-membered ring in the synthesis of pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **II**.

III.1.a. Method IIA

According to this approach, the starting 1,3-disubstituted 6-alkyluracil **40** is transformed into 6-(α-bromoalkyl) derivative **41** *via* bromination in chloroform or dichloromethane followed by condensation with primary amines. This results in the corresponding pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **42** (Scheme 16).[63 – 65]

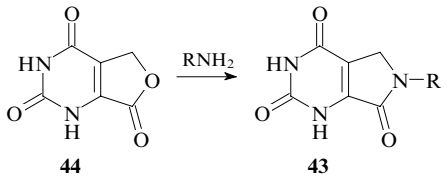
One more reaction which may be attributed to the same type has been reported by Britikova *et al.*[66] The authors

Scheme 16



obtained pyrrolo[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-triones **43** by the reaction of 5-hydroxymethylorotic acid lactone **44** with ammonia, amines or their hydrochlorides, proceeding in ethylene glycol at 180 °C for 2 h. The yields of the aminolysis products ranged widely from 36% to 96%. The highest yields were detected when using substituted anilines (Scheme 17).

Scheme 17



R = H, Bu^n, Bn, $(CH_2)_2OH$, CH_2CO_2Et, $(CH_2)_2CO_2Et$, CH_2CO_2H, $(CH_2)_2CO_2H$, Ph, C_6H_4OMe-4, C_6H_4Cl-4

III.1.b. Method IIB

Zimmerman *et al.*[67] developed a one-step synthetic procedure to obtain pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones starting from the 1,3-disubstituted uracil. 1,3-Dibenzyluracil (**45a**; $R^1 = R^2 = H$) was treated with a threefold excess of NaH and 1.5-fold excess of *p*-toluenesulfonylmethyl isocyanide (TsMIC) in ether at 0 °C to give 1,3-dibenzylpyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**46**) in 91% yield (Scheme 18). The similar results were obtained by Mařák *et al.*[6] and by Carvalho *et al.*[68]

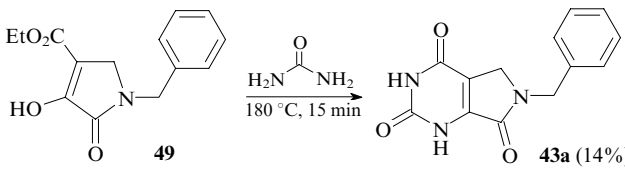
Ono *et al.*[69] used ethyl isocyanidoacetate (**48**), an analogue of TsMIC, to form a pyrrole ring in the synthesis of pyrrolo[3,4-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione **47**. As a starting compound, the authors used 1,3-bis-(4-methoxybenzyl)-5-nitrouracil (**45b**; $R^1 = NO_2$, $R^2 = OMe$) (see Scheme 18).

III.2. Closure of a pyrimidine ring

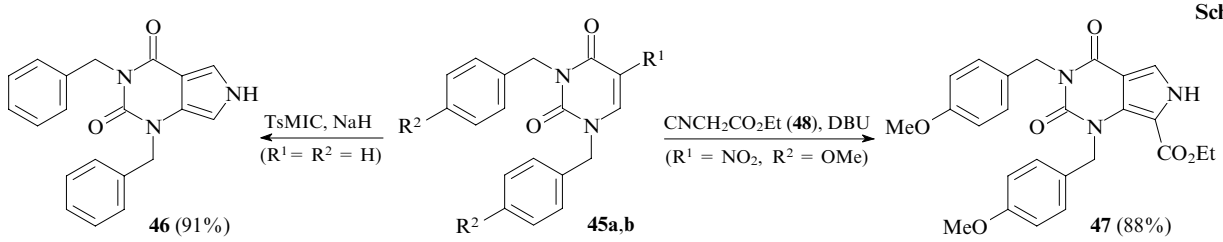
There are only few known reactions proceeding with the formation of a pyrimidine ring and affording heterocyclic system **II**, because the starting aminopyrroles are difficult to obtain.

For instance, Southwick and Hofmann [70] obtained 6-benzylpyrrolo[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione (**43a**) by fusing 1-benzyl-3-hydroxy-4-ethoxycarbonyl-2-oxo-1,5-dihy-

Scheme 19



Scheme 18



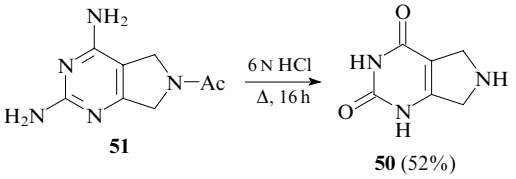
DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene

dropyrrole (**49**) and a 20-fold molar excess of urea at 180 °C for 15 min (Scheme 19).

III.3. Modification of a pyrimidine ring

To synthesize 5,7-dihydropyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**50**), Sheradsky and Southwick [71] hydrolyzed 2,4-diamino derivative **51** by refluxing in HCl for 16 h (Scheme 20).

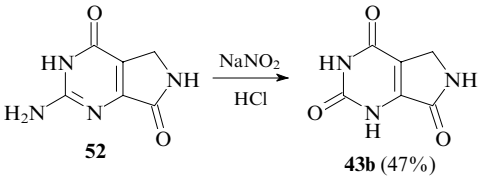
Scheme 20



51 **50** (52%)

The synthesis of pyrrolo[3,4-*d*]pyrimidine-2,4,7(1*H*,3*H*,5*H*)-trione (**43b**) by treating 2-aminopyrrolo[3,4-*d*]pyrimidine-4,7(3*H*,5*H*)-dione (**52**) with sodium nitrite in an acidic medium has been described [70] (Scheme 21).

Scheme 21

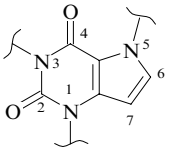


52 **43b** (47%)

IV. Pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones

Pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **III** are also deaza analogues of xanthine as they contain a carbon atom instead of the nitrogen atom in the 7-position. They are the most studied compounds compared with the isomeric heterocycles **I** and **II**.

Structure III



III

IV.1. Closure of a pyrrole ring

Among approaches to form a pyrrole ring in the synthesis of heterocyclic system **III**, four groups of methods can be distinguished depending on the type of the bonds formed (Fig. 3):

1) N(5)–C(6) and C(6)=C(7) (method **IIIA**);
2) N(5)–C(6) and C(7)–C(7a) (method **IIIB**);
3) N(5)–C(6) (method **IIIC**);
4) C(7)–C(7a) (method **IIID**).

IV.1.a. Method IIIA

The pyrrole ring closure according to type **IIIA** is one of the most popular methods in the synthesis of pyrrolo[3,2-*d*]-pyrimidine-2,4(1*H*,3*H*)-diones. All the methods resulting in the formation of this heterocyclic system can be subdivided into two groups comprising:

1) synthesis of 6-methyl-5-nitrouracil derivative having an alkene moiety in position 6, reduction of the nitro group and cyclization;

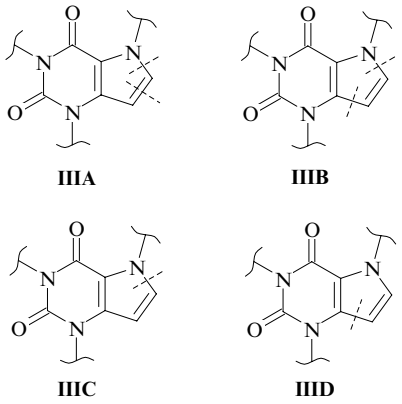
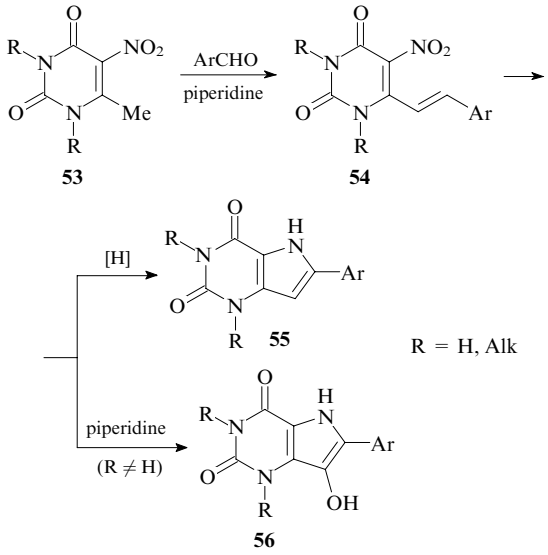


Figure 3. Types of formation of a five-membered ring in the synthesis of pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **III**.

2) alkylation of 6-methyl-5-nirouracil yielding 6-alkyl derivatives followed by a pyrrole ring closure under the action of a base.

According to the first route, the key step is the condensation of equimolar amounts of 1,3-dialkyl-6-methyl-5-nitrouracil **53** with aromatic aldehyde in the presence of 1.5-fold molar excess of piperidine and 3 Å molecular sieves.[11–13,72–75] The reaction produces good yields of 6-styryl derivatives of uracil **54** transforming subsequently into 6-aryl substituted pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **55** *via* nitro group reduction and pyrrole ring closure (Scheme 22).

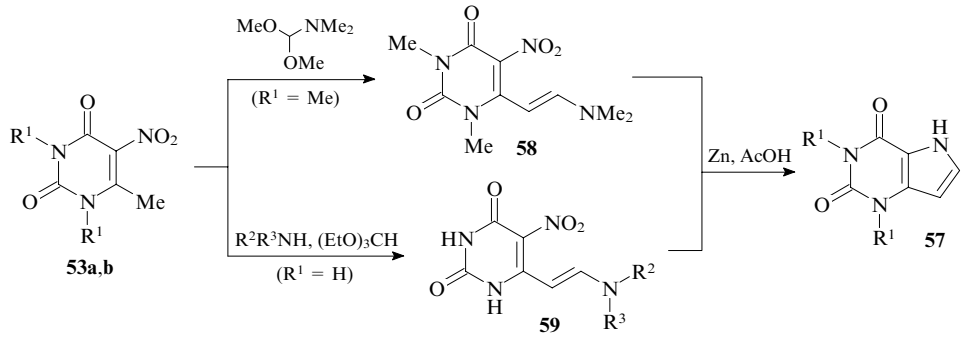
Scheme 22

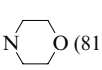


53 **54** **55** **56**

The NO_2 group in 1,3-dialkyl-6-methyl-5-nitrouracils is reduced using various reagents and reaction conditions. For example,[11,12,72] the nitro group was reduced with a twofold excess of sodium dithionite in formic acid. Also, the use of stannous chloride in DMF was described.[73,74] Furthermore, reduction of the NO_2 group on refluxing the reaction mixture with an excess of triethyl phosphite was also reported.[13,73,75] The last-mentioned approach gives substantially lower yields of the desired heterocycles due to a moderate solubility of 6-styryluracils in triethyl phosphite.

Scheme 23



53: R^1 = H (**a**), Me (**b**); R^2R^3N = Ph_2N (43% yield), MePhN (55%),  (73%),  (81%)

Yoneda *et al.*[76] prepared 7-hydroxypyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **56**. The starting 1,3-disubstituted 6-methyl-5-nitrouracils **53** were condensed with a threefold excess of an aromatic aldehyde in DMF in the presence of piperidine as a base. This gave the desired heterocycles **56** in moderate (42% – 52%) yields by oxidation – reduction mechanism. This synthetic approach to pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones occurs only when the starting uracil has substituted nitrogen atoms: compound **53a** (R = H) does not react (see Scheme 22).

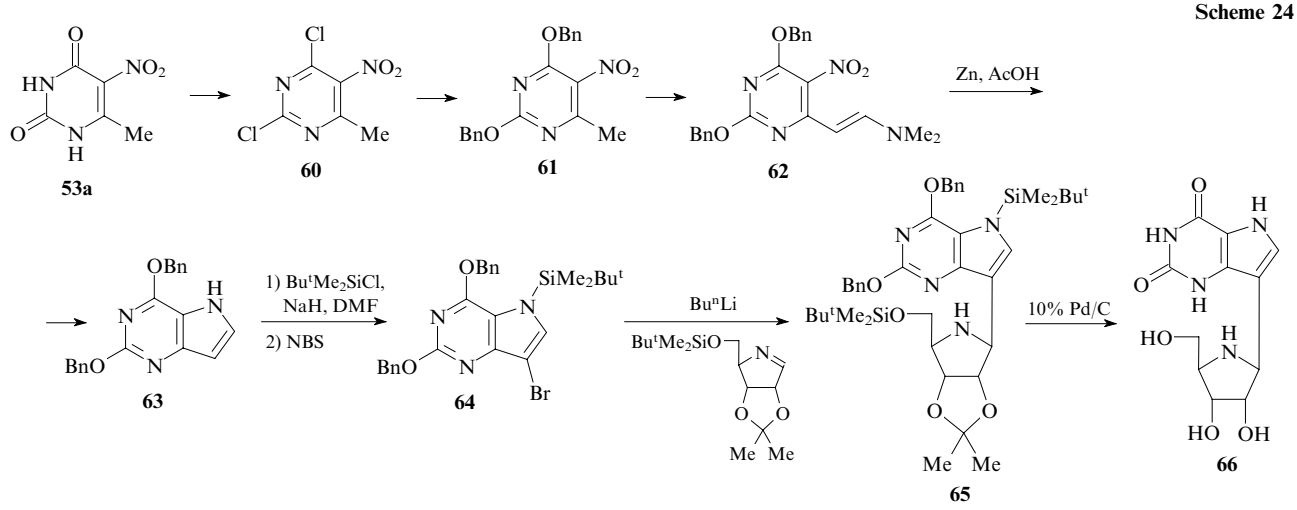
To obtain pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **57** having no substituents in position 6, a different method has been proposed (Scheme 23).[77] In this case, 1,3,6-trimethyl-5-nitrouracil (**53b**) is first transformed into the 6-(2-dimethylaminovinyl) derivative **58**, and the subsequent reduction produces the desired product. 6-(2-Aminovinyl)-5-nitrouracil **59** is obtained in two ways from 6-methyl-5-nitrouracil (**53a**). The first one compises heating to reflux in a triethyl orthoformate solution in the presence of a threefold excess of a secondary amine,[78] and the second one includes treatment with the DMF acetal in anhydrous DMF with heating. In the second case, the yield of product **59** ($R^2 = R^3$ = Me) is 81%.[79, 80] The reduction of 6-(2-aminovinyl)-5-nitrouracils **59** with zinc powder in acetic acid at 70 – 80 °C produces pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **57** in 65% – 82% yields (see Scheme 23).

Evans *et al.*[81] obtained a number of 9-deazapurine-derived aza-C-nucleosides, analogues of immucillin, which is a purine phosphorylase inhibitor.[82] First, 6-methyl-5-nitrouracil (**53a**) was converted to 2,4-dichloro-6-methyl-5-nitropyrimidine (**60**) and then to 2,4-dibenzyloxy derivative **61**, which was used without further purification in the condensation reaction to give 2,4-dibenzyloxy-6-[2-(*N*,*N*-dimethylamino)vinyl]-5-nitropyrimidine (**62**). The product yield over two steps was 73% (Scheme 24).

The nitro group in compound **62** was reduced with zinc powder in acetic acid at temperature below 50 °C. The reaction produced 2,6-dibenzyloxy-9-deazapurine (**63**) in 78% yield. Silylation of the N(7) atom and the subsequent bromination with *N*-bromosuccinimide (NBS) afforded 9-bromo-2,6-dibenzyloxy-7-(*tert*-butyldimethylsilyl)-9-deazapurine (**64**) in 57% yield. Metallation of this compound with n-butyllithium at −70 °C in a 2 : 3 anisole – diethyl ether mixture followed by condensation with a cyclic imine gave aza-C-nucleoside **65** (41% yield). Deprotection by hydrogenolysis in ethanol followed by heating in MeOH in the presence of concentrated HCl resulted in the desired pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione nucleoside **66** as the hydrochloride (57% yield).

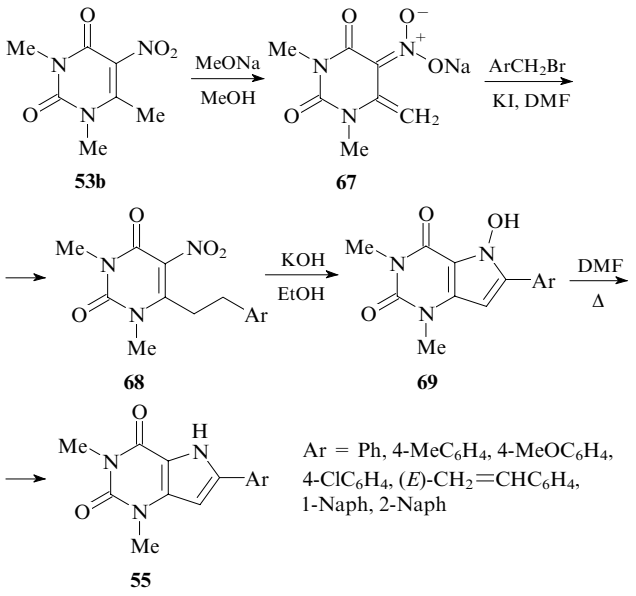
Another procedure according to method **IIIA** is based on using 1,3,6-trimethyl-5-nitrouracil (**53b**) as the starting compound.[83, 84] Under the action of sodium methoxide, it gives the salt **67** and the subsequent treatment with arylmethyl bromide in DMF yields the 6-(2-arylethyl)-5-nitro uracil derivative **68**. Closure of the pyrrole ring is induced by KOH in ethanol and gives 6-aryl-5-hydroxy-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **69**, which are converted to 6-aryl-1,3-dimethylpyrrolo[3,2-*d*]pyrimi-

Scheme 24



dine-2,4(1*H*,3*H*)-diones **55** on heating in DMF for 2 h. The product yields vary widely, the lowest ones being detected for 6-(2-naphthyl) (31%) and 6-[(*E*)-styryl] derivatives (63%). Meanwhile, 6-phenyl and 6-(1-naphthyl) derivatives were obtained in nearly quantitative yields (84%–95%) (Scheme 25).

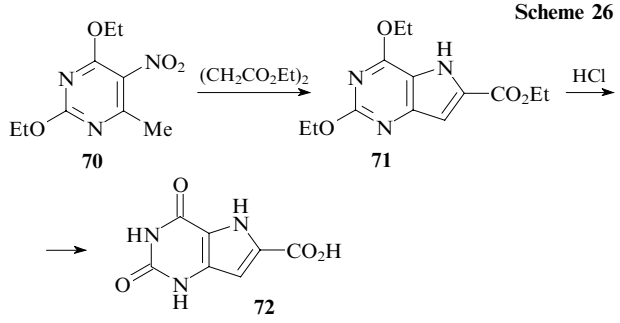
Scheme 25



53b **67** **68** **69** **55**

The condensation of 2,4-diethoxy-6-methyl-5-nitropyrimidine (**70**) with diethyl succinate followed by hydrolysis of 2,4-diethoxypyrrolo[3,2-*d*]pyrimidine **71** also relates to method **IIIA** (Scheme 26).[85] The authors do not report the yield of the target pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione-6-carboxylic acid (**72**).

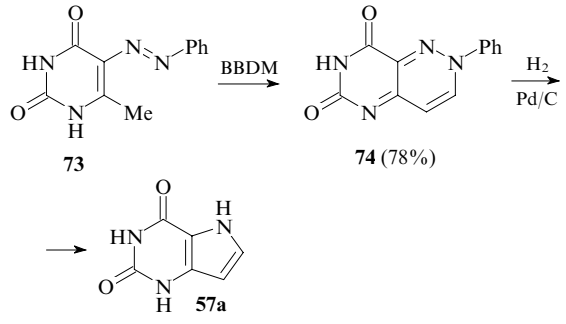
Scheme 26



70 **71** **72**

The preparation of pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**57a**) is another example of type **IIIA** synthesis (Scheme 27). Treatment of the starting 6-methyl-5-phenylazouracil (**73**) with an excess of *tert*-butoxybis(dimethylamino)methane (BBDM) in DMF on heating at 60–65 °C affords 2-phenylpyrimido[5,4-*c*]pyridazine-6,8(2*H*,7*H*)-dione **74**, the catalytic hydrogenation of which in the presence of 10% Pd/C in AcOH gives the desired product **57a** in 62% yield.[86]

Scheme 27

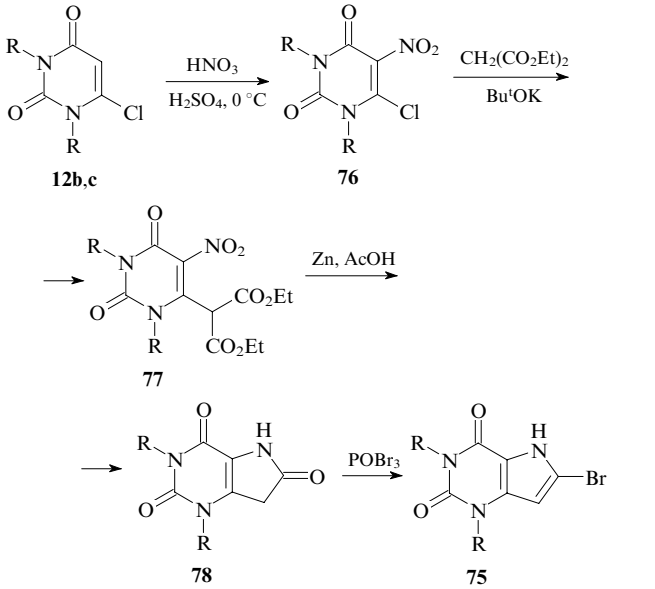


73 **74** (78%) **57a**

IV.1.b. Method IIIB

Bartoccini *et al.*[87] developed a synthetic procedure for the preparation of 1,3-dialkyl-6-bromopyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **75**, which are convenient intermediates to introduce various substituents *via* a cross-coupling reaction. The desired compounds were obtained from 1,3-dialkyl-6-chlorouracils **12** [R = Me (**b**), Et (**c**)], which were converted to 1,3-dialkyl-6-chloro-5-nitrouracils **76** upon nitration with a mixture of sulfuric and nitric acids at 0 °C. Compounds **76** were treated, without further purification, with a 1.2-fold excess of diethyl malonate in dioxane in the presence of a twofold molar excess of potassium *tert*-butoxide. The diethyl 2-(1,3-dialkyl-5-nitro-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)malonates **77** formed were subjected to nitro group reduction on treatment with Zn in AcOH at 120 °C. The overall yield of 1,3-dialkylpyrrolo[3,2-*d*]pyrimidine-2,4,6-(1*H*,3*H*,7*H*)-triones **78** was 45%–48%. On treatment with a threefold molar excess of $POBr_3$, they were converted to 6-bromo derivarives **75** in 90%–92% yields (Scheme 28).

Scheme 28



12b,c **76** **77** **78** **75**

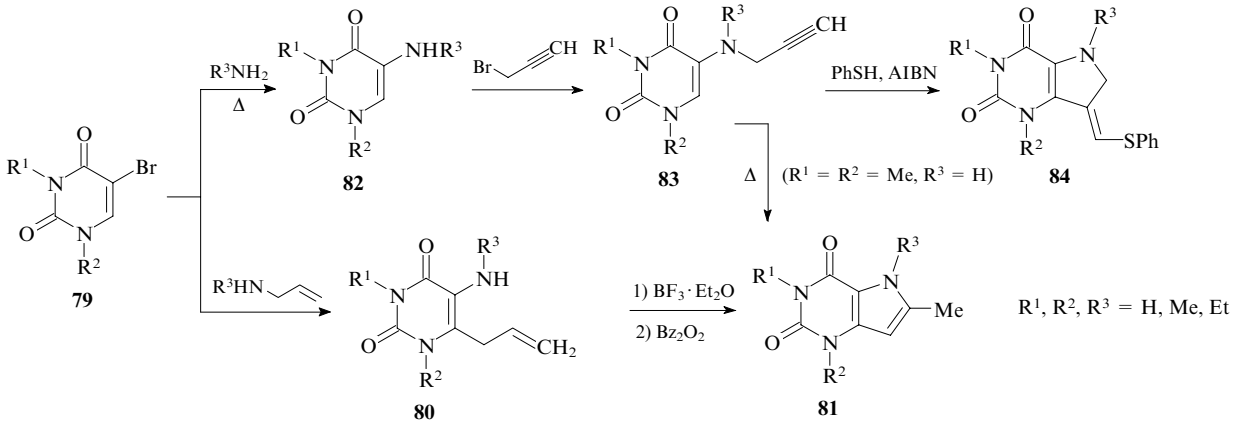
R = Me, Et

IV.1.c. Method IIIC

Majumdar and Mondal[88] have performed amination of 1,3-disubstituted 5-bromouracil **79** with a fivefold molar excess of allylamine or its *N*-derivatives (Scheme 29). The Claisen rearrangement of 1,3-disubstituted 5-allylaminouracils **80** and subsequent radical cyclization on refluxing in DMF for 3 h in the presence of benzoyl peroxide afforded pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **81** in 95%–99% yields.

Kawahara *et al.*[50] proposed a convenient synthetic approach to pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **81** *via* a pyrrole ring closure (see Scheme 29). First, the treatment of 5-amino-1,3-dimethyluracil **82** ($R^1 = R^2 =$ Me, $R^3 = H$) with propargyl bromide in a 1:1 MeOH–

Scheme 29



CH_2Cl_2 mixture at room temperature afforded 1,3-dimethyl-5-propargylaminouracil **83** ($R^1 = R^2 = Me$, $R^3 = H$) in 41% yield, which was refluxed in DMF under N_2 for 40 h to give the desired compound **81** ($R^1 = R^2 = Me$, $R^3 = H$) in 64.6% yield.

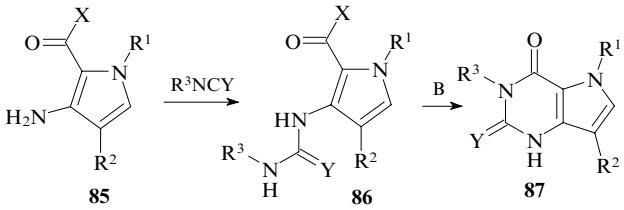
IV.1.d. Method IIID

Majumdar *et al.*[89] reported the synthesis of 6,7-dihydropyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **84** based on oxidative closure of a pyrrole ring in the presence of benzenethiol (see Scheme 29). The starting 1,3-disubstituted 5-(propargylamino)uracil **83** was obtained *via* amination of 1,3-disubstituted 5-bromouracil **79** with methyl- or ethylamine in aqueous ethanol followed by the treatment of the corresponding 5-aminouracil **82** with propargyl bromide in acetone in the presence of K_2CO_3.[90] 5-(Propargylamino)uracil **83** was refluxed under N_2 in *tert*-butanol in the presence of a twofold molar excess of benzenethiol and 1.5-fold molar excess of azobis(isobutyronitrile) (AIBN). The yield of the desired (*E*)-1,3,5-trialkyl-7-[(phenylsulfanyl)methylidene]-6,7-dihydropyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **84** was 60% – 65%.

IV.2. Closure of a pyrimidine ring

Most methods for pyrimidine ring closure described in the literature for the synthesis of pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones involve the use of isocyanates or isothiocyanates. For example, 3-amino-2-ethoxycarbonyl and 3-amino-2-carbamido derivatives of pyrrole **85** are condensed with an excess of alkyl or aryl (iso)cyanate in an inert solvent affording the corresponding (thio)urea derivatives **86** (Scheme 30).[91 – 93] Closure of a pyrimidine ring is carried out in the presence of a base. This gives pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones and their thio analogues **87** in good yields.

Scheme 30

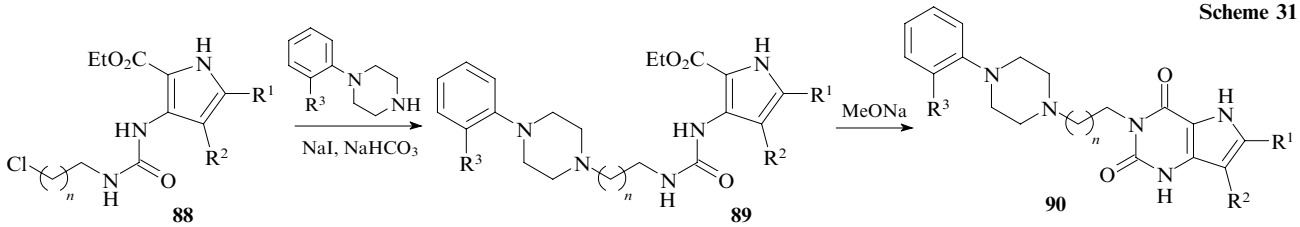


X = OEt, NH_2; Y = O, S; R^1 = H, Bn; R^2 = Me, CN, CO_2Et; R^3 = Alk, All, Bn, Ph, 4-MeC_6H_4

There are several versions of this approach. Patanè *et al.*[94] and Pittala *et al.*[95] pretreated the intermediate ethyl 5-aryl-3-[3-(ω-chloroalkyl)ureido]-1*H*-pyrrole-2-carboxylate (**88**)[96] with a 1.5-fold molar excess of *N*-arylpiperazine in THF in the presence of NaI and $NaHCO_3$ to give *N*-arylpiperazino derivatives **89**. The latter were treated with sodium methoxide in methanol, which resulted in substituted pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **90** in 36% – 79% yields (Scheme 31).

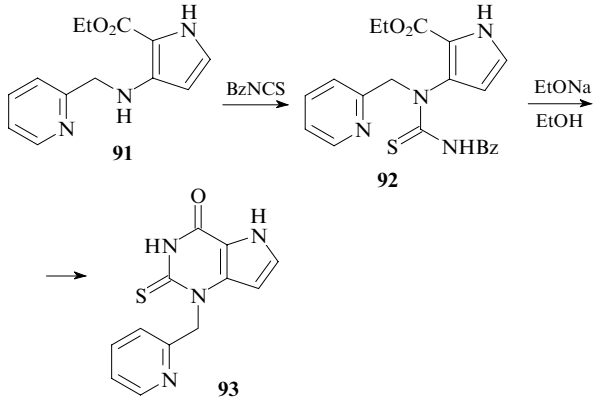
The use of alkyl or aryl iso(thio)cyanates in this reaction results finally in 3-substituted pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones. Malmquist *et al.*[97] developed a synthetic procedure to obtain 1-substituted heterocycles (Scheme 32). This approach is based on the reaction between ethyl 3-[(2-pyridylmethyl)amino]pyrrole-2-carboxylate (**91**) and benzoyl isothiocyanate. The resulting ureide **92** cyclizes in the presence of sodium ethoxide to give the desired 1-(2-pyridylmethyl)-2-thioxo-1,2-dihydropyrrolo[3,2-*d*]pyrimidine-4(3*H*)-one (**93**). However, the overall yield of the product is as low as 8.5%.

Scheme 31



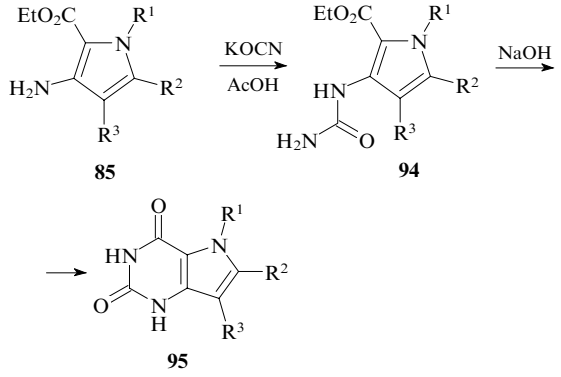
R^1 = H, Ph, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BnO, 4-$PhO(CH_2)_2O$, 2-Fu; R^2 = H, Ph, 2-ClC_6H_4, 4-ClC_6H_4; R^3 = Cl, MeO; *n* = 1, 2; Fu is furyl

Scheme 32



To obtain pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones having no substituents at the nitrogen atoms of the pyrimidine moiety, sodium cyanate was proposed (Scheme 33). Condensation of KOCN with 3-aminopyrrole-2-carboxylates **85** (X = OEt) was carried out in aqueous acetic acid. Intermediate compounds **94** were treated with NaOH in water to give the desired heterocycles **95** in 51%–77% yields.[17,98]

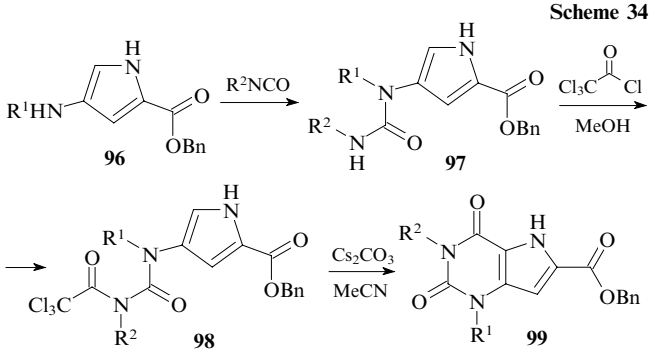
Scheme 33



R^1 = H, 2-CN-5-FC_6H_3; R^2 = Ph, piperidino; R^3 = H, CO_2Bu^t

An unusual synthetic route to pyrrolo[3,2-*d*]pyrimidine heterocyclic system has been described by Marcotte *et al.*[99] (Scheme 34). The method is based on the condensation of 4-aminopyrrole-2-carboxylic acid ester **96** with an equimolar amount of isocyanate in dichloromethane at room temperature. The yield of products **97** was rather high (88%–99%). Acylation of **97** with an excess of trichloroacetyl chloride in acetonitrile at 80 °C followed by treatment

Scheme 34

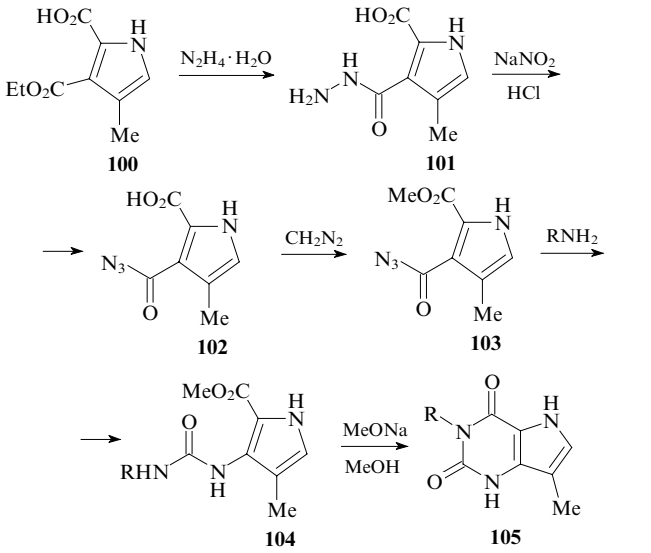


R^1, R^2 = Et, Pr^i, All, Bn, Ph

of intermediates **98** with an excess of Cs_2CO_3 results in pyrimidine ring closure to give target pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **99** in 53%–79% yields.

A somewhat different approach was suggested by Garcia-Lopez *et al.*[100] (Scheme 35). The authors heated the starting pyrrole **100** at reflux with an excess of hydrazine hydrate in ethanol for 8 h. The hydrazide **101** formed was treated with an aqueous solution of $NaNO_2$ in the presence of hydrochloric acid at 0 °C, resulting in 3-azidocarbonyl derivative **102**. Its reaction with diazomethane in 1,2-dimethoxyethane produced 2-methoxycarbonyl derivative **103**, which was heated in benzene with an equimolar amount of ammonia, methylamine or aniline. The corresponding 3-ureido deivatives **104** were obtained in overall yields of 15%–30%. The pyrimidine ring closure was accomplished by refluxing in methanol in the presence of sodium methoxide. The yield of the target 3-substituted 7-methylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **105** ranged between 47% and 62%.

Scheme 35

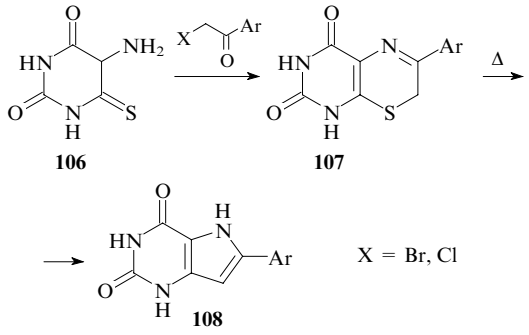


R = H, Me, Bn, Ph

IV.3. Other methods

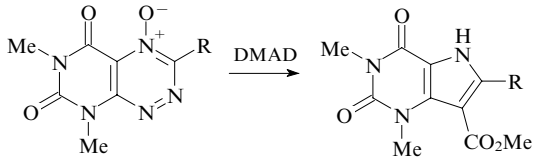
Fenner and Motschall[101] found that treatment of 5-amino-6-thiobarbituric acid (**106**) with phenacyl chloride or bromide afforded 6-arylpyrimido[4,5-*b*][1,4]thiazines **107**. The latter eliminate sulfur quantitatively to be converted to the corresponding pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **108** on heating in DMF at 130 °C for 3–4 h (Scheme 36). The authors gave no mention of the yields.

Scheme 36



An interesting domino reaction is initiated by 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate (DMAD) to N-oxides of alkyl derivatives of fervenulin **109**. Heating these compounds with a 1.5-fold molar excess of DMAD in toluene at 95 °C produces 6-alkyl-1,3-dimethyl-7-methoxycarbonylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **110** in yields of 55% – 64% (Scheme 37).[102, 103]

Scheme 37



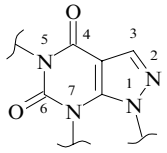
109 **110**

R = H, Me, Et

V. 1*H*-Pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones

1*H*-Pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **IV** are isomers of xanthines as they comprise a pyrazole ring, instead of imidazole one, annulated to a pyrimidine-2,4-dione system. It should be noted that the atom numbering in these heterocycles differs from that for the above deaza-xanthines.

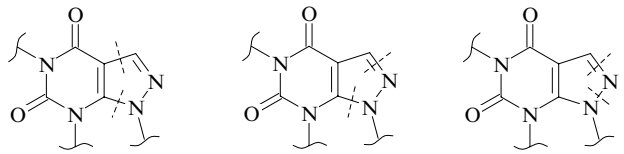
Structure IV



IV

V.1. Closure of a pyrazole ring

The synthetic approaches to 1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones based on pyrazole ring closure may be arbitrarily subdivided into three groups in terms of the cyclization method (Fig. 4). The first two methods (**IVA** and **IVB**) are most popular as they require synthetically the most accessible pyrimidine component. Method **IVC** has a more limited preparative application; only a few such reactions of practical interest have been described in literature.



IVA **IVB** **IVC**

Figure 4. Types of formation of a five-membered ring in the synthesis of 1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **IV**.

V.1.a. Method IVA

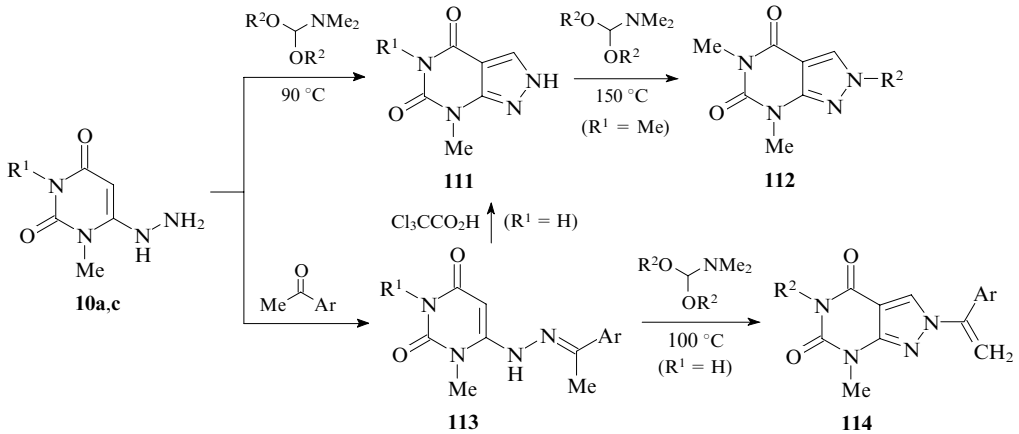
This approach to the design of heterocyclic system **IV** implies the use of 6-hydrazino-1,3-dimethyluracils **10a**,**c** [R^1 = H (**c**), Me (**a**)] as the starting compounds, which can be obtained easily *via* condensation of the corresponding 6-chlorouracil with hydrazine hydrate.[104] For the subsequent closure of a pyrazole ring, various condensing agents are applied. The nature of the condensing agent depends directly on the type of substituent to be introduced into position 3 of the pyrazole moiety (Scheme 38).

Thus, treatment of 1,3-disubstituted 6-hydrazinouracil **10a** with DMF acetal under mild conditions (90 °C, 30 min) affords 2*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**111**) having no substituents at the pyrazole nitrogen atoms (66% yield).[105] On continuing the process under more drastic conditions (150 °C, 90 min), DMF dialkyl acetal acts as an alkylating agent and produces finally 2,5,7-trialkylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **112** (R^2 = Alk) in 61% – 82% yields.

Upon condensation with benzophenones, hydrazinouracils **10a**,**c** are converted to hydrazones **113**. Subsequent treatment of compounds **113** (R^1 = H) with trichloroacetic acid gives heterocycle **111** (R^1 = H) in 88% yield.[106]

When hydrazones **113** were heated with an excess of DMF dimethyl or diethyl acetal under more drastic conditions (140 °C, 12 h), pyrazole ring closure was observed (see Scheme 38). Furthermore, DMF acetal was noticed to act as an alkylating agent. The yield of 2,5,7-trimethyl-substituted pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **114** (R^1 = R^2 = Me) was 67% – 83%, whereas 5-ethyl deriv-

Scheme 38

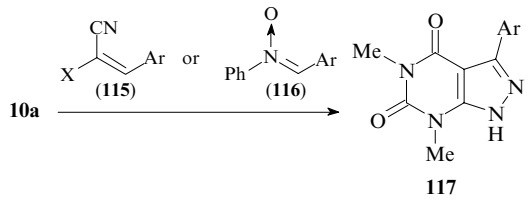


R^1 = H, Me; R^2 = Me, Et, Pr^n, Bu^n

atives **114** (R^2 = Et) were obtained in lower yields (40% – 68%).[106]

Bhuyan *et al.* used a threefold excess of cyanoalkene **115** (see Ref. 107) or an equimolar amount of nitrone **116** (see Ref. 108) to carry out the condensation with 6-hydrazinouracil **10a** (Scheme 39).

Scheme 39

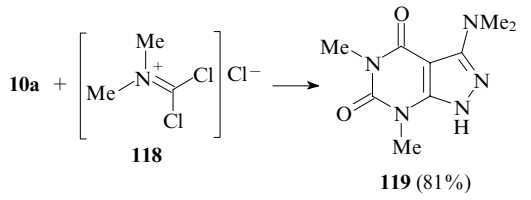


Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, Bn, 2-Fu, 2-Th;
X = CN, CO_2Et, $C(O)NH_2$; Th is thienyl

Pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **117** bearing an aromatic or heteroaromatic substituent at position 3 were synthesized in this way. In the former case, the yields of the products were 82% – 92%, while in the latter case, they were 85% – 96%.

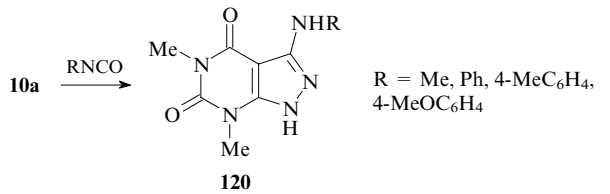
Among reagents used for the pyrazole ring closure, mention should be made of *N*,*N*-dimethyldichloroiminium chloride (**118**), which is successfuly applied in the synthesis of various heterocyclic systems including pyrazolo[3,4-*d*]-pyrimidine-4,6(5*H*,7*H*)-diones. The condensation of 6-hydrazino-1,3-dimethyluracil **10a** with the chloride **118** affords rather readily 3-dimethylamino-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**119**) (Scheme 40).[109]

Scheme 40



Alkyl and aryl isocyanates find wide application in the synthesis of pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones. For example, condensation of 6-hydrazinouracil **10a** with these reagents gives the desired heterocycles **120** having a secondary amino group in position 3 (Scheme 41).[110, 111] The yield of these products is sufficiently high (80% – 95%).

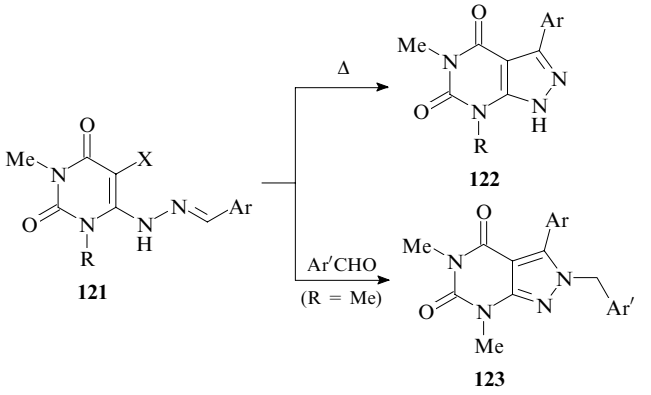
Scheme 41



The use of alkyl and aryl isothiocyanates for pyrazole ring closure was reported.[112, 113] The reactions gave also 3-amino-substutited pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **120**, although in noticeably lower yields (< 28%).

Several more procedures according to method **IVA** are used to synthesize 1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones bearing an aromatic substituent in position 3 of the pyrazole moiety. All of the procedures are based on the use of arylhydrazones **121** (X = H), which are pre-synthesized by treating 6-hydrazinouracils with the corresponding aromatic aldehyde.[104] The subsequent thermolysis under drastic conditions (260 – 300 °C) affords 3-aryl-substituted pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **122** (Scheme 42). However, the yields were low because of side reactions (35% – 45%).[104]

Scheme 42



R = H, Me; Ar, Ar′ = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3,4-$Cl_2C_6H_3$, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 4-$Me_2NC_6H_4$;
X = H, Br, NO_2

For this reason, preference is given to a method which makes use of 6-(arylidenehydrazino)uracil derivatives bearing a good leaving group in position 5. Kanazawa *et al.*[114] synthesized 3-aryl-substituted 5,7-dimethylpyrazolo[3,4-*d*]-pyrimidine-4,6(5*H*,7*H*)-diones **122** by treating the starting 6-(arylidenehydrazino)-1,3-dimethyluracil **121** (R = Me, X = H) with *N*-bromosuccinimide. As a result, 6-(2-arylidenehydrazino)-5-bromo-1,3-dimethyluracil **121** (R = Me, X = Br) was obtained in a good yield and cyclized rapidly to give pyrazole **122**. The yields of the target compounds **122** were 63% – 81%.

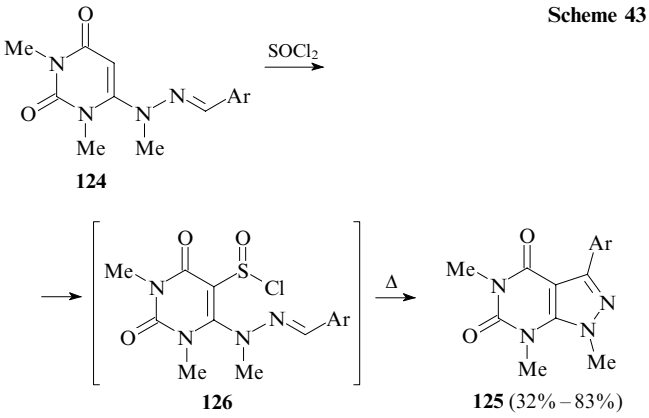
The NO_2 group is also a good leaving group. In this procedure according to method **IVA**, 6-(benzylidenehydrazino)-1,3-dimethyl-5-nitrouracil **121** (R = Me, X = NO_2) was used as the starting compound, which was easily obtained by treatment of 6-chloro-1,3-dimethyl-5-nitrouracil with phenylhydrazone (see Scheme 42).[115, 116]

To obtain pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione derivatives having substituents in positions 2 and 3 of the pyrazole moiety, Yoneda *et al.*[117] condensed 6-(benzylidenehydrazino)-1,3-dimethyluracil **121** (R = Me, X = H) with an excess of an aromatic aldehyde, which furnished pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **123** in 58% – 87% yields. The lowest product yield (32%) was obtained with cinnamaldehyde.

Senga *et al.*[118] found that thionyl chloride can also be a good condensing agent. Treating 6-(benzylydene-1-methylhydrazino)-1,3-dimethyluracil **124** with this agent afforded 3-aryl-1,5,7-trimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **125** in 32% – 83% yields. Supposedly, the original reaction products were 5-sulfinyl derivatives **126**, which were converted to compounds **125** on heating (Scheme 43).

Takahashi *et al.*[119] obtained 1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione **127** bearing a CF_3 group in position 3 by the reaction between 1,3-dimethyl-6-(1-methylhydrazino)uracil (**10b**) and a twofold molar excess of trifluoroacetic

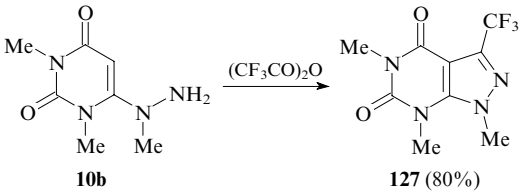
Scheme 43



Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$

anhydride in the presence of 1 equiv. of lutidine (Scheme 44).

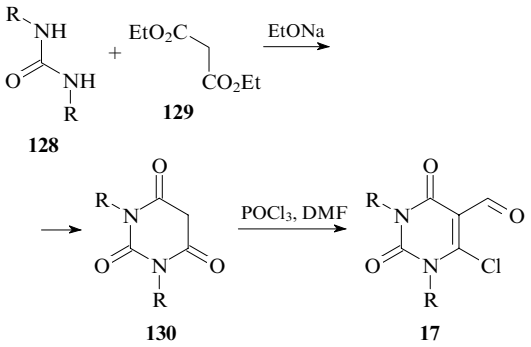
Scheme 44



V.1.b. Method IVB

According to the approach discussed in this section, the formation of the pyrazole part of a molecule is accomplished by the addition of the N – N moiety to a pyrimidine component bearing an appropriate substituent in position 5. For this purpose, the most-used are 1,3-di-5-formyl-6-chlorouracils **17** obtainable *via* a two-step synthesis.[120] The first step is condensation of *N*,*N*′-dialkyurea **128** with malonic ester **129** (or malonic acid) affording 1,3-dialkyl derivatives of barbituric acid **130**, while the subsequent formylation using the Vilsmeier reagent results in the products **17** in yields of up to 90% (Scheme 45).

Scheme 45

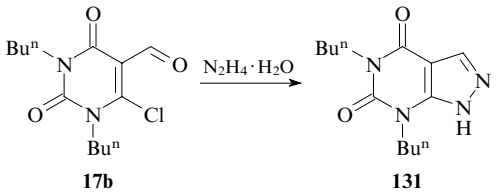


R = H, Alk

Basing on this approach, Gilbert *et al.*[120] synthesized 6-chloro-1,3-di-n-butyl-5-formyluracil (**17b**), which was then condensed with hydrazine hydrate. The desired pyrazolopyrimidine **131** was isolated in 60% yield (Scheme 46).

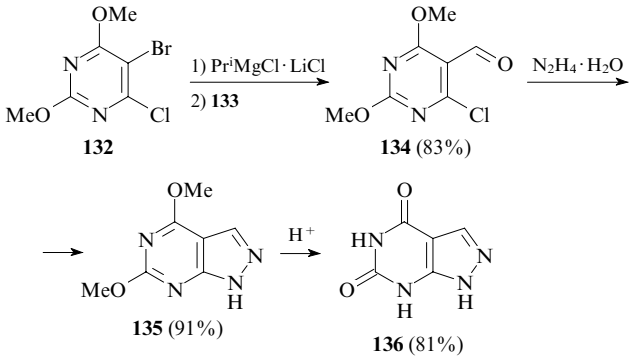
It is known that to retain the amide moieties during the formylation of barbituric acid with the POCl$_3$ – DMF system, the uracil nitrogen atoms are usually protected by various groups, which are subsequently difficult to remove.

Scheme 46



Boudet and Knochel[121] developed an effective synthetic procedure for the preparation of pyrazolo[3,4-*d*]pyrimidine-4,6-(5*H*,7*H*)-dione having no substituents at the nitrogen atoms (Scheme 47). This method implies using 5-bromo-6-chloro-2,4-dimethoxypyrimidine (**132**) as the starting compound, which is obtained *via* bromination of 6-chloro-2,4-dimethoxypyrimidine. Compound **132** is made to react first with the Grignard reagent and subsequently with *N*-formylmorpholine (**133**). This affords 4-chloro-2,6-dimethoxypyrimidine-5-carbaldehyde (**134**). Condensation of the latter with an excess of hydrazine hydrate affords 4,6-dimethoxy-1*H*-pyrazolo[3,4-*d*]pyrimidine (**135**), which is converted to the desired pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**136**) upon the subsequent acid hydrolysis.

Scheme 47

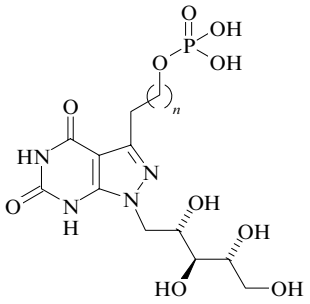


A similar approach was applied by Zhang *et al.*[122] in the synthesis of pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones bearing various substituents in positions 1 and 3. Compounds of this series exhibit inhibitory activities towards lumazine synthase from *Mycobacterium tuberculosis* and may be considered as potental antitubercular agents. For example, metallation of the starting 4-chloro-2,6-dimethoxypyrimidine with n-butyllithium in THF followed by the condensation of the Li salt with the ω-(phosphoryloxy)alkanecarboxylates affords 5-keto derivatives. Treating them with hydrazine hydrate yields pyrazolo[3,4-*d*]pyrimidine-4,6-diones, which undergo alkylation and subsequent acid hydrolysis to give ribityl-substituted pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **137**. The yields of the products for $n = 3$ and 4 were 37.0% and 25.7%, respectively, and for $n = 2$ the target compound was obtained in a quantitative yield.

In the synthesis of pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones by method **IVB**, not only 6-chloro-5-formyluracils but the parent barbituric acids having a carbonyl functionality in position 5 can be used as starting compounds. Faidallah and Khan[123] reported condensation of 5-trifluoroacetyl derivatives of barbituric and 2-thiobarbituric acids **138** with hydrazine hydrate (Scheme 48). As a result, the corresponding 3-trifluoromethyl derivatives of

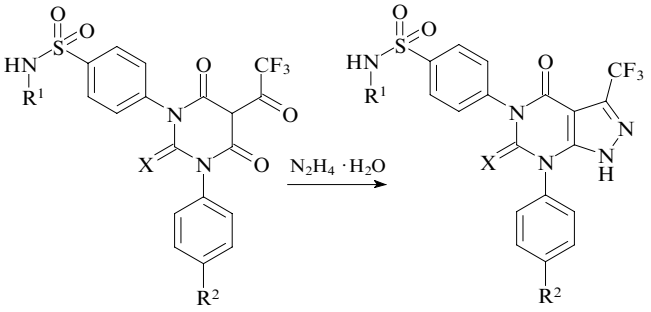
5,7-diarylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **139** were obtained.

Structures 137



137 (n = 2–4)

Scheme 48

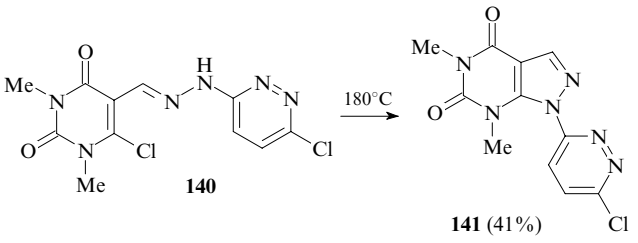


138 **139** (64%–69%)

R^1 = H, Ac, 4-phenylimidazol-2-yl, 5-oxo-4,5-dihydroimidazol-2-yl; R^2 = H, Cl; X = O, S

The reaction between 1,3-dialkyl-6-chloro-5-formyluracils and hydrazines bearing various substituents at the nitrogen atoms may produce mixtures of 1- and 2-substituted heterocycles depending on the reaction conditions and the nature of the substituent in hydrazine.[124] Therefore, precondensation of hydrazines at the formyl group is more favourable in terms of regioselectivity of the pyrazole ring closure. Thermolysis of 6-chloro-5-formyl-1,3-dimethyluracil hydrazone (**140**) at 180 °C affords exclusively the 1-(6-chloropyridazin-3-yl) derivative of 5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**141**) (Scheme 49).[125]

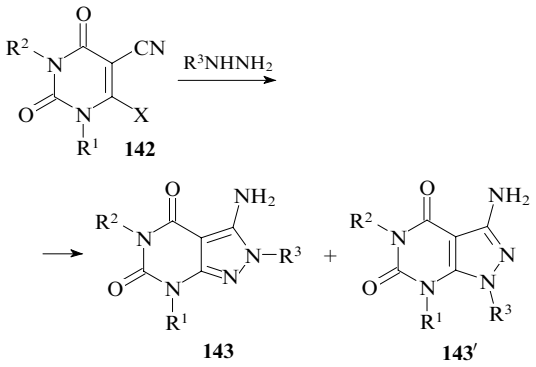
Scheme 49



140 **141** (41%)

For a pyrazole ring closure, the use of 6-chloro-5-cyanouracil derivatives **142** (R^1 = R^2 = H, X = Cl) instead of compounds having a 5-formyl group has been patented.[113] However, here again, the reaction between uracil and substituted hydrazines may result in a mixture of 1- and 2-substituted 3-aminopyrazolo[3,4-*d*]pyrimidine-4,6-(5*H*,7*H*)-diones **143** and **143′** (Scheme 50).

Scheme 50



142 **143** **143′**

R^1, R^2 = H, Me, Pr^i, Bu^n; R^3 = H, Ph; X = Cl, SMe, CN

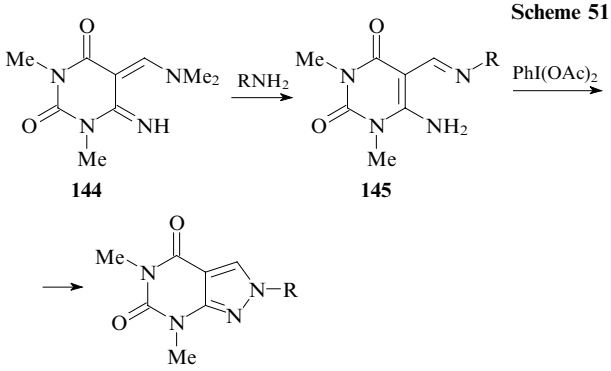
The methylsulfanyl substitutent can also be a good leaving group. Tominaga *et al.*[126] synthesized 3-aminopyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **143** in 88% yield by condensation of 5-cyano-6-(methylsulfanyl)uracil **142** (R^1 = R^2 = H, X = SMe) with hydrazine hydrate or phenylhydrazine.

5,6-Dicyano-1,3-dimethyluracil **142** (R^1 = R^2 = Me, X = CN) was also used as the starting compound in the synthesis of 3-amino-5,7-dimethylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **143**. This dicyano derivative was obtained by treating of 6-chloro-5-cyano-1,3-dimethyluracil with sodium cyanide. The 6-cyano group may be easily replaced by various nucleophiles. On condensation with a twofold molar excess of hydrazine hydrate, the target heterocycle **143** is formed in a yield close to quantitative (94%).[127]

V.1.c. Method IVC

Method **IVC** is used very rarely in the synthesis of the heterocyclic system in question. The advantage of this method is that exclusively 2-substituted pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **112** are formed. Monguchi *et al.*[128] and Sajiki *et al.*[129] synthesized heterocycles **112** starting from 6-imino-1,3-dimethyl-5-[(dimethylamino)methylidene]-5,6-dihydropyrimidine-2,4(1*H*,3*H*)-dione (**144**), which is readily obtained from 6-amino-1,3-dimethyluracil under the action of $POCl_3$—DMF system. Imino derivatives **144** were first treated with an excess of amine to give 5-iminomethyl derivatives **145** and then with iodobenzene diacetate. The pyrazole ring is closed in the oxidation step

Scheme 51



144 **145** **112** (40%–97%)

R = Me, Bu^t, Bu^n, cyclo-C_5H_9, cyclo-C_6H_{11}, Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 1-Naph

(Scheme 51); the target compounds **112** were obtained in yields of 40% – 97%.

V.2. Closure of a pyrimidine ring

An alternative approach to the preparation of 1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones and their thio analogues is the formation of a pyrimidine ring on the basis of 3-aminopyrazole-4-carboxylic acid derivatives. These methods can be subdivided into three groups according to the reagents in use:

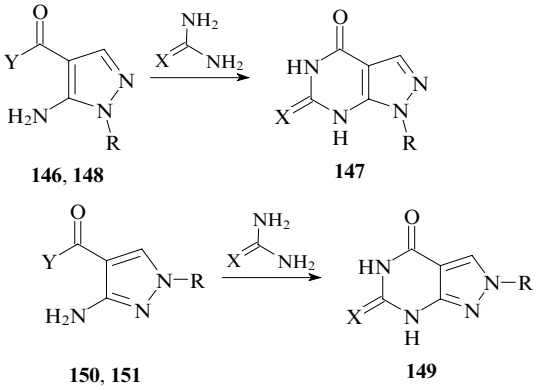
1) fusion with urea or thiourea;
2) condensation with alkyl or aryl isocyanates;
3) condensation with carbon disulfide or xanthates.

The first two methods are more common; they served to prepare a large number of 1*H*-pyrazolo-[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones.

V.2.a. Reactions with (thio)urea

This method is valuable because it can provide pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione derivatives having no substituents in the pyrimidine moiety. For example, fusion of 3-aminopyrazole-4-carboxamide **146** (Y = NH_2) with an excess of urea or thiourea results in the desired heterocycles **147** (Scheme 52).

Scheme 52



146, **148** **147**

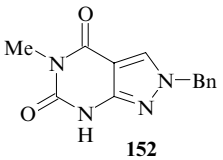
150, **151** **149**

X = O, S; R = H, Alk, Ar; Y = NH_2 (**146**, **150**), OEt (**148**, **151**)

Later, it was shown that, aside from 3-aminopyrazole **146** bearing an amide functionality,[2, 130 – 132] 3-aminopyrazole **148** having an ester functionality is also well suited for forming the pyrimidine-4,6(5*H*,7*H*)-dione part of molecule **IV** by fusion with urea and thiourea.[3, 4, 133 – 135]

A similar approach makes it possible to synthesize 2-substituted pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **149** using 1-substituted 3-aminopyrazoles **150** and **151** as starting compounds.[3, 135] Fusion of 3-aminopyrazole **151a** (R = Bn) with an excess of *N*,*N*′-dimethylurea resulting in the formation of 5-methylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione **152** has been reported.[135] However, the product yield was as low as 42.9%. The synthesis of 5-substituted pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones similar to compound **152** using isocyanates is far more effective (see below).

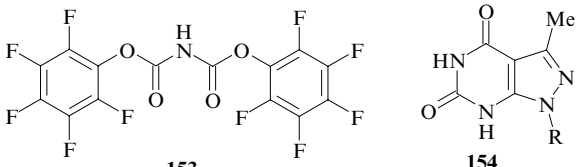
Structure 152



152

The properties similar to those of urea derivatives are inherent in bis(pentafluorophenyl)imidodicarbonate **153**. which was proposed for forming an uracil moiety.[136] Thermolysis at 250 °C and sonication of 3-amino-5-methylpyrazoles substituted at position 2 in the presence of reagent **153** afforded the corresponding pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **154** in yields of 51% (R = Me) and 53% (R = Ph).

Structures 153, 154



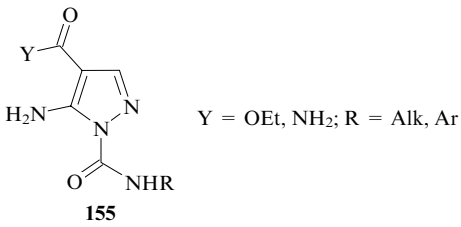
153 **154**

R = Me, Ph

V.2.b. Reactions with iso(thio)cyanates

Isocyanates and isothiocyanates find fairly wide application in the synthesis of 5-alkyl- or aryl-substituted 1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones. The starting compounds are commonly aminopyrazolecarboxylic acid derivatives **146**, **148** [3, 135] or **150**, **151** [3, 21, 135, 137 – 139] bearing various substituents at the nitrogen atoms of the heterocycle. The original condensation products of such aminopyrazoles with isocyanates and isothiocyanates are ureides or thioureides, respectively, forming a pyrimidine ring on treatment with bases. 5-Aminopyrazole-4-carboxylic acids unsubstituted at the heterocyclic nitrogen atom do not form ureides when react with isocyanates; instead, they form carbamoyl derivatives of pyrazole **155**.

Structures 155



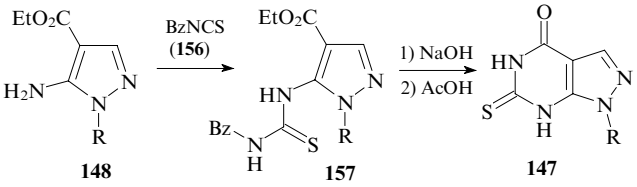
155

Y = OEt, NH_2; R = Alk, Ar

However, there has been reported [26] the possibility to use unsubstituted ethyl 3-aminopyrazole-4-carboxylates **148** (R = H) in the reaction with various isothiocyanates (but not with isocyanates!). The corresponding thioureides were treated with a 5% NaOH solution under reflux to afford 5-substituted 6-thio analogues of pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones in yields of 65% – 82%.

Carraro *et al.*,[140] and Manetti *et al.*[141] described the condensation of aminopyrazoles **148** with benzoyl isothiocyanate (**156**) to give benzoylthioureids **157**, which were converted to 5-unsubstituted 6-thio analogues of pyra-

Scheme 53



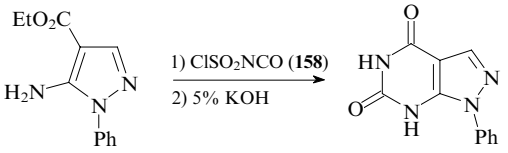
148 **157** **147**

R = $CH_2CH(OH)Ph$, $CH_2CH(OH)C_6H_4F$-4, $CH_2CH(OH)C_6H_4Cl$-4

zolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **147** (X = S) in yields from 70% to 80% on treatment with alkali and subsequent hydrolysis (Scheme 53).

One more procedure of condensation of aminopyrazoles with isocyanates giving 1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones with unsubstituted nitrogen atoms in the pyrimidine ring has been developed by Wamhoff and Ertas.[142] The authors condensed aminopyrazole **148a** with chlorosulfonyl isocyanate (**158**) and then treated the reaction mixture with alkali. This furnished the desired heterocycle **147a** in 86% yield (Scheme 54).

Scheme 54

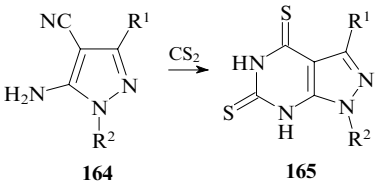


El Haddad *et al.*[143] converted pyrazole-3,4-dicarboxylic acid monoester (**159**) first to the acid chloride by the action of an excess of ethyl chloroformate and then to acyl azide **160** under the action of NaN_3. Next, compound **160** was refluxed in 1,2-dimethoxyethane with 1.2 equiv. of the corresponding aniline. The basis for this reaction is the Curtius rearrangement in which acyl azide **160** is transformed on heating into isocyanate **161**, which reacts with anilines. This method was used to prepare a series of compounds **162** (80% – 92% yield). The pyrimidine ring was closed *via* intramolecular condensation in the presence of sodium ethoxide (85% – 95%). A distinctive feature of the above approach is that the isocyanate moiety is a part of the pyrazole component reacting with amine. Nevertheless, as in the previous cases, the transformation results in the formation of 5-substituted heterocycles, namely 5-aryl-1,3-diohenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **163** (Scheme 55).

V.2.c. Condensation with carbon disulfide

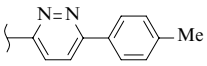
Numerous studies (see, *e.g.* Refs 138, 144 – 146) describe the reaction of 2-substituted 3-amino-4-cyanopyrazoles **164** with carbon disulfide in the presence of alkali (Scheme 56) to afford pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dithiones **165** in yields ranging from 32% to 80%.

Scheme 56



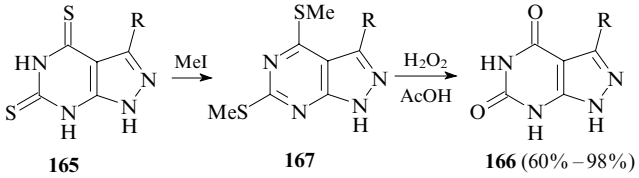
R^1 = H, Me, Et, SMe, CN, CO_2Et, C(O)NHPh, Ac, Bz,

C(O)C_6H_4Me-4, NHPh; R^2 = Ph, Bz, Ts,



Tominaga *et al.*[147] developed a synthetic procedure to transform dithiones **165** into the corresponding 3-substituted pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **166**. The procedure implies treatment of compounds **165** with methyl iodide followed by the oxidation of 4,6-bis(methylsulfanyl)pyrazolo[3,4-*d*]pyrimidines **167** with a 30% hydrogen peroxide solution in acetic acid (Scheme 57).

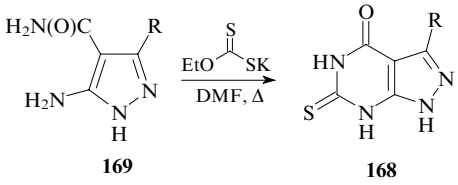
Scheme 57



R = Ph, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, Bn

Bontems *et al.*[148] reported the synthesis of 6-thio analogues of pyrazolo[3,4-*d*]pyrimidinediones **168** in 89% – 91% yield *via* the condensation of 5-aminopyrazolecarboxamide **169** with a threefold molar excess of potassium xanthate in DMF with heating (Scheme 58).

Scheme 58



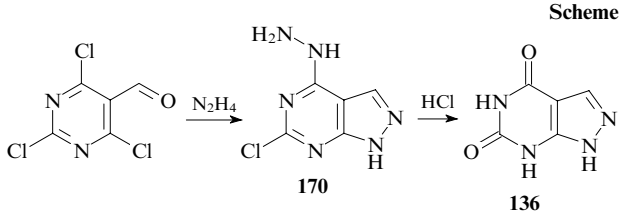
R = Me, Ph

V.3. Miscellaneous methods

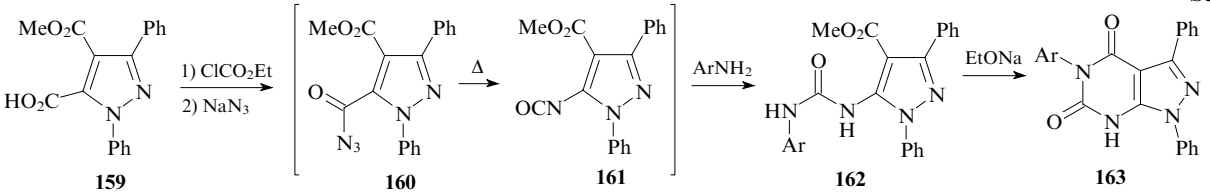
Among other synthetic procedures to obtain pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-diones, mention should be made of those comprising the transformations of functionalities in positions 2 and 4 of the pyrimidine moiety such as hydrolysis and enzymatic oxidation.

Thus, Nagamatsu, Fujita and Endo[149, 150] proposed a synthetic approach to unsubstituted pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**136**) based on treatment of the starting 2,4,6-trichloropyrimidine-5-carbaldehyde with an

Scheme 59



Scheme 55

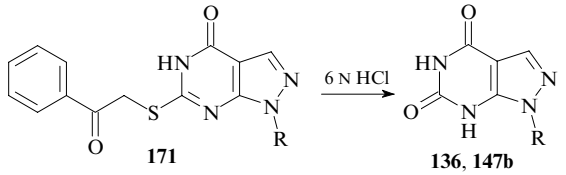


Ar = Ph, 2-MeC_6H_4, 2-EtC_6H_4, 3-ClC_6H_4, 4-$MeOC_6H_4$, 2-Py; Py is pyridyl

excess of hydrazine. As a result, intermediate 6-chloro-4-hydrazinopyrazolo[3,4-*d*]pyrimidine (**170**) is formed, which is then refluxed in concentrated hydrochloric acid. The desired pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**136**) was obtained in 58% yield (Scheme 59).

Hydrolysis of compounds **171**, namely, 6-phenacylsulfanylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione and its 1-methyl derivative has been described.[16] Products **136** and **147b** are formed on refluxing in an ethanol–dioxane solution in the presence of concentrated hydrochloric acid (Scheme 60).

Scheme 60

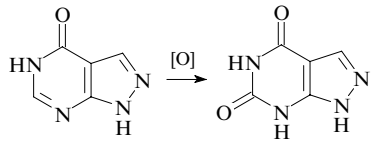


171 **136**, **147b**

R = H (**136**), Me (**147b**)

A number of papers report the use of xanthine oxidase in oxidation of allopurinol (**172**) to obtain pyrazole[3,4-*d*]-pyrimidine-4,6(5*H*,7*H*)-dione **136** (Scheme 61).[151 – 153] Similarly to the previous example, the authors do not give the yield of the product.

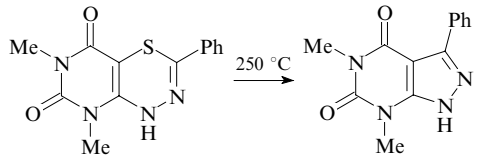
Scheme 61



172 **136**

Ichiba and Senga[154] synthesized 3-phenylpyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**174**) by thermolysis of a fused thiadiazine **173** at 250 °C. The desired compounds were obtained in the yields close to quantitative (Scheme 62). However, this synthetic procedure has considerable drawbacks because of low availability of the starting thiadiazine.

Scheme 62

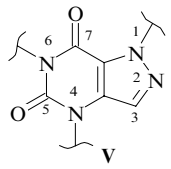


173 **174** (97%)

VI. 1*H*-Pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-diones

1*H*-Pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-diones **V** differ from the heterocyclic system **IV** by the type of annulation between pyrimidine and pyrazole rings. These compounds are isomers of xanthines in the position of the nitrogen atoms in the five-membered moiety.

Structure V

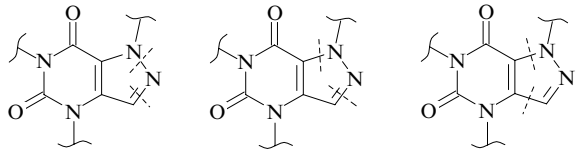


V

VI.1. Closure of a pyrazole ring

Only few synthetic approaches to 1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-diones **V** based on the pyrazole ring closure in pyrimidinedione derivatives have been reported. Nevertheless, all presently known cyclization methods may be arbitrarily subdivided into three groups according to the type of the bonds formed (Fig. 5):

1) N(1) – N(2) and N(2) = C(3) (method **VA**);
2) C(7a) – N(1) and N(2) = C(3) (method **VB**);
3) C(7a) – N(1) and C(3) – C(3a) (method **VC**).



VA **VB** **VC**

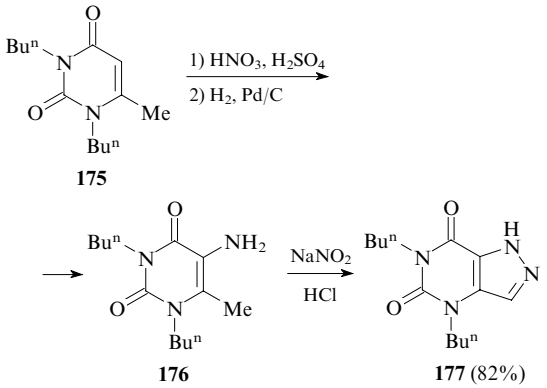
Figure 5. Types of formation of a five-membered ring in the synthesis of 1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-diones **V**.

VI.1.a. Method VA

This is the most facile route to 1*H*-pyrazolo-[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-dione. Behrend[155] pioneered in describing the synthesis of this heterocyclic system *via* cyclization of 5-amino-6-methyluracil as early as in 1888 (though without experimental details). Practical implementation of this method was performed by Gilbert *et al.*,[120] and the concept of synthesis of the starting 1,3-disubstituted 6-methyluracils was suggested by Egg and Volgger.[156]

Thus, 1,3-di-n-butyl-6-methyluracil (**175**) was treated with a mixture of nitric and sulfuric acids. The intermediate 5-nitro derivative (96% yield) was hydrogenated over Pd/C in ethyl acetate at 23 °C. As a result, 5-amino derivative **176** was obtained in 56% yield; on treatment with $NaNO_2$ in hydrochloric acid at 0 °C for 30 min, it was converted to 4,6-di-n-butylpyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**177**) (Scheme 63).[156]

Scheme 63



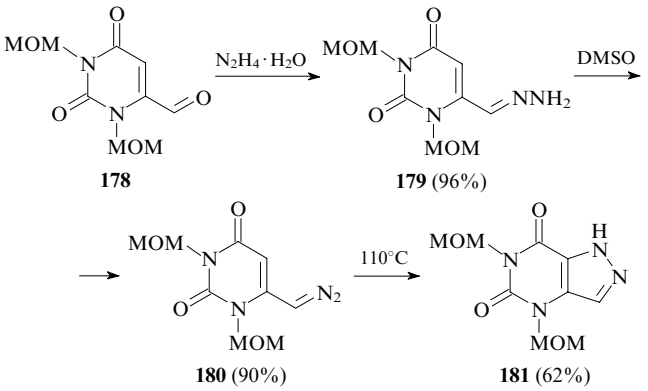
175 **176** **177** (82%)

VI.1.b. Method VB

This method differs from the above one by the opposite order of the bond formation in the pyrazole ring. This method is illustrated by the study of Zhang *et al.*[157] First,

6-methyluracil bearing 1- and 3-methoxymethyl protective groups was oxidized with SeO_2 to produce 6-carbaldehyde **178**.[158] Condensation of the latter with hydrazine hydrate afforded hydrazone **179**, which was oxidized with DMSO to give 6-diazomethyl uracil derivative **180**. Its thermolysis in boiling toluene furnished annulated pyrazole **181** (62% yield after sublimation). The protective groups were removed by treating compound **181** with boron tribromide at −78 °C to give the target product in 55% yield (Scheme 64).

Scheme 64

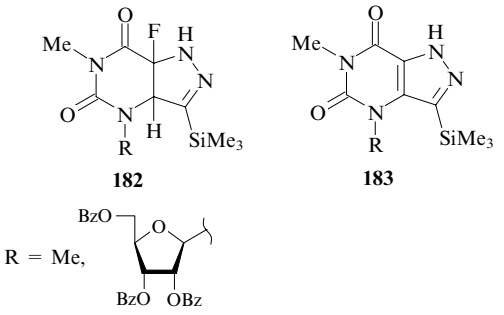


MOM is methoxymethyl

VI.1.c. Method VC

The third synthetic approach to pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-dione derivatives **V** described in literature includes the addition of a $C^- - N^+ \equiv N$ type synthon to the C(5)=C(6) double bond of the uracil. It should be noted that thus far this method has been of limited practical interest. There are only few examples of preparative synthesis of such derivatives. For example, Saladino *et al.*[159] performed the pyrazole ring closure by treatment of 1,3-dimethyl-5-halogenouracils and their 1-glycosylated analogues with the Li salt of trimethylsilyldiazomethane [$Me_3SiC(Li)N_2$], which was obtained *in situ* by the action of n-butyllithium on Me_3SiCHN_2. As a result, the fluorides transformed into the corresponding dihydropyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-diones **182** (68% and 63% yields), while bromides gave 3-trimethylsilylpyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-diones **183** (54% and 78% yields).

Structures 182, 183

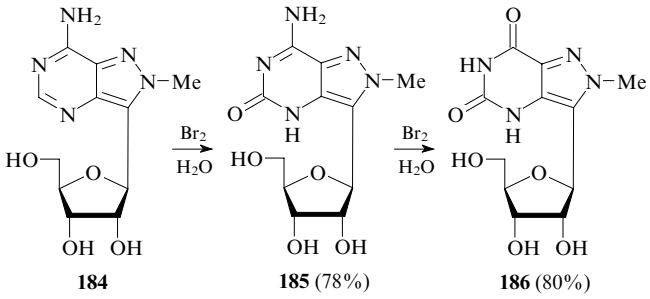


In the presence of other substituents in position 5 of uracil (*e.g.*, nitro group or hydrogen atom), the isolated mixture of condensation products required chromatographic separation.

VI.2. Modification of a pyrimidine ring

Ugarkar *et al.*[160] synthesized nucleoside analogues based on the pyrazolo[4,3-*d*]pyrimidine system **V**. 7-Amino-2-methyl-3-(β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine (**184**, 2-methylformycin) was treated twice with bromine water yielding first 7-amino-2-methyl-3-(β-D-ribofuranosyl)pyrazolo[4,3-*d*]-pyrimidine-5(4*H*)-one (**185**) and then 2-methyl-3-(β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**186**) (Scheme 65). Alternative conditions for the second step of the synthesis of compound **186**, *i.e.* treatment with nitrosyl chloride in DMF at 0 °C, have been proposed; in this case, the yield of the product was 60%.

Scheme 65



VI.3. Closure of a pyrimidine ring

The pyrimidine ring formation on the basis of 4-aminopyrazole-5-carboxylic acid derivatives is one more approach to pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-diones **V**. As in the previous sections, all published methods of such synthesis can be subdivided into two groups according to the reagents in use:

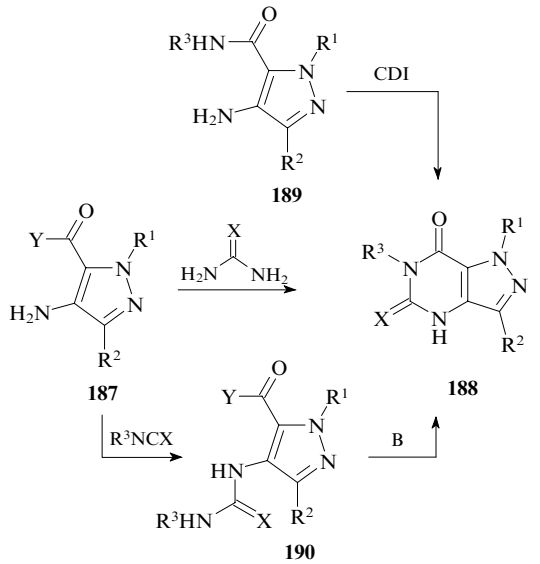
1) reactions with carbonyl-containing reagents;

2) condensation with alkyl or aryl isocyanate and their thio analogues.

VI.3.a. Reactions with carbonyl-containing reagents

4-Aminopyrazol-5-carboxamides **187** can be successfully fused with an excess of urea or thiourea.[14,161] Pyrazolo[4,3-*d*]pyrimidines **188** (R^3 = H) are formed in 55% to quantitative yields (Scheme 66).

Scheme 66



R^1, R^2, R^3 = H, Me, Pr^n, Pr^i, $(CH_2)_3Ph$; X = O, S; Y = NH_2, OEt

A method based on the use of 1,1′-carbonyldiimidazole (CDI) to form a pyrimidine ring has been described.[22, 23, 25, 162] Treating the starting 4-amino-1*H*-pyrazole-5-carboxamide **189** with 1,1′-carbonyldiimidazole in boiling acetonitrile gives the target heterocycle **188** (R^1 = H, Me; R^2 = Me; R^3 = H; X = O) in high yield (see Scheme 66).

There are methods for pyrimidine ring closure based on the use of phosgene (heating in toluene in a sealed tube)[24] and triphosgene.[15]

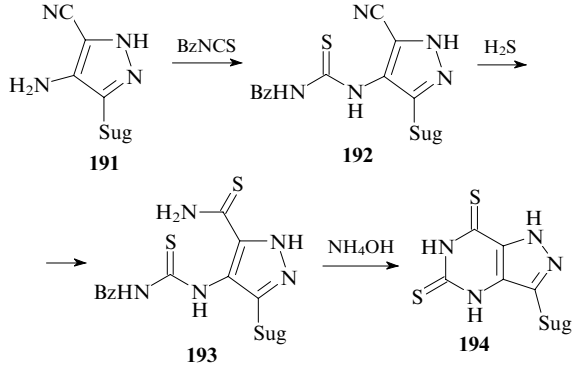
VI.3.b. Condensation with iso(thio)cyanates

A convenient synthetic procedure to obtain 6-substituted azolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-diones **188** using iso(thio)cyanates has been developed. In this procedure, 4-aminopyrazole-5-carboxylic acid amides[163] or ethyl esters[164] were used as the starting compounds and ureidopyrazoles **190** were formed as intermediates. The condensation of compounds **187** with isocyanates or isothiocyanates was carried out in the presence of a base (see Scheme 66).

Synthesis of 6-aryl-1,3-diphenylpyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **188** (X = O, R^1 = R^2 = Ph, R^3 = Ar) *via* a sequence of chemical transformations similar to that illustrated in Scheme 55 has been described.[143]

To obtain 6-unsubstituted pyrazolo[4,3-*d*]pyrimidine-5,7(4*H*,6*H*)-diones, Acton and Ryan[165] developed an approach comprising the condensation of 4-aminopyrazole-5-carbonitrile **191** with benzoyl isothiocyanate. This gave thioureide **192**, which was converted to the corresponding 5-carbothioamide **193** under the action of H_2S. Treatment of product **193** with an alkali gave the target C-nucleoside **194** (Scheme 67). The yields of the final products, *i.e.* nucleoside analogues, have not been reported.[165]

Scheme 67



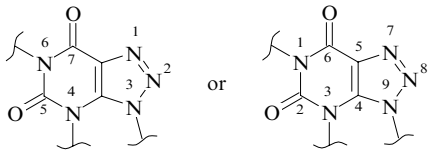
191 **192** **193** **194**

Sug is D-ribofuranosyl, 2-deoxy-D-ribofuranosyl, D-arabinofuranosyl

VII. 3*H*-[1,2,3]Triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones

3*H*-[1,2,3]Triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (8-azapurines, **VI**) possess interesting biological properties. (It should be noted that in some studies, these compounds are treated as purine analogues and the corresponding atom numbering is used.) In particular, nucleosides comprising 8-azapurine as a base were found to have cytostatic activity towards a series of tumours in cell cultures.[6] 8-Azaxanthine was found to have antibacterial activity[166] and inhibitory activity towards protozoa *Typanosoma cruzi*.[167]

Structure VI

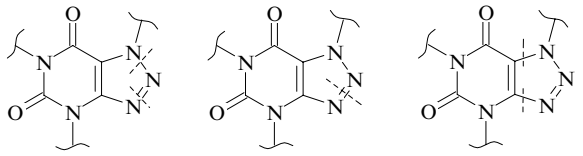


VI **VI**

VII.1. Closure of a 1,2,3-triazole ring

To obtain a heterocyclic system of 8-azapurines **VI**, triazole ring closure is widely used. The methods are classified according to the type of the bonds formed (Fig. 6):

1) N(1)–N(2) and N(2)=N(3) (method **VIA**);
2) N(2)=N(3) (method **VIB**);
3) C(7a)–N(1) and N(3)–C(3a) (method **VIC**).



VIA **VIB** **VIC**

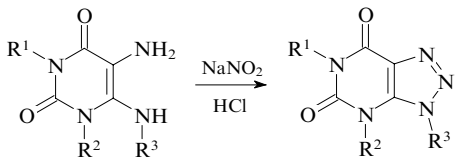
Figure 6. Types of formation of a five-membered ring in the synthesis of 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones **VI**.

VII.1.a. Method VIA

Derivatives of 5,6-diaminouracil are the most common starting compounds to construct a 1,2,3-triazole ring annulated to a pyrimidinedione system. In this case, nitrous acid generated *in situ* acts as a condensing agent and a source of the nitrogen atom in position 2 of diaminouracil.

The study of Blicke and Godt[1] is among the first reports concerning the possibility of triazole ring closure in 5,6-diamino-1,3-dimethyluracil **195** (R^1 = R^2 = Me, R^3 = H). After treatment of the starting compound with sodium nitrite in hydrochloric acid, the authors obtained 1,3-dimethyl-2,6-dioxo-8-azapurine **196** (R^1 = R^2 = Me, R^3 = H) in 81% yield. Similar products were synthesized later by Nübel and Pfleiderer[168] (Scheme 68).

Scheme 68

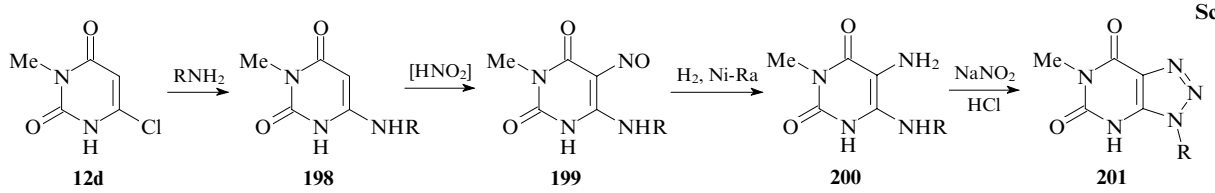


195 **196**

R^1, R^2, R^3 = H, Me, Et, $(CH_2)_2OH$, Bn

At the same time the authors cited[168] demonstrated that 6-amino-5-benzylaminouracils do not form the corresponding 7-benzyl-8-azaxanthines under the same conditions. These reactions produced 6-amino-5-(*N*-benzylamino-*N*-nitroso) uracil derivatives **197**.

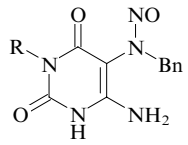
Scheme 69



12d **198** **199** **200** **201**

R = Me, Et, Pr^n, Bu^n, Bn

Structures 197



197

R = H, Me

When substituted 6-aminouracil serves as the starting compound, a sequence of reactions of 5-nitrosation and nitroso group reduction is used to introduce an amino group into position 5.

A modification of this approach to produce 9-substituted 8-azaxanthines has been proposed by Bozóvá *et al.*[169] This method is based on amination of 6-chloro-3-methyluracil (**12d**) with an alkylamine performed in an autoclave at 120 – 130 °C for 8 h. The intermediate 6-alkylaminouracil **198** was nitrosated in two ways: using either $NaNO_2$ in acetic acid at 70 °C or propyl nitrite in the presence of a catalytic amount of hydrochloric acid in ethanol. The nitroso group in compound **199** was reduced by the Raney nickel (Ni-Ra) in aqueous medium. The 5,6-diamino derivative **200** thus formed was dissolved in hydrochloric acid and treated with $NaNO_2$ solution at 10 °C. The yield of 9-alkyl-1-methyl-8-azaxanthines **201** ranged between 43% and 54% (Scheme 69).

Nogueras *et al.*[7, 170] used this approach to synthesize a series of nucleoside analogues comprising 8-azaxanthine as a base. A synthetic value of such procedure has been also confirmed by Islam and Nagamatsu [171] as well as by other authors,[172, 173] who obtained a number of alkyl-substituted 1*H*- and 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones in yields from 60% to 94%.

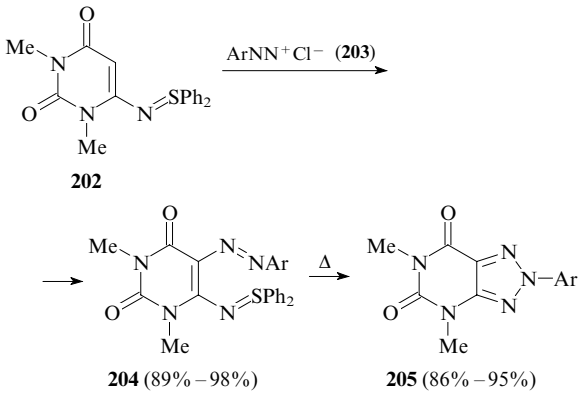
Kraas *et al.*[174] used 6-chloro-5-nitropyrimidine as the starting compound in the synthesis of 8-azapurines. This compound was condensed with an amine and then the nitro group was reduced. The 5,6-diamino pyrimidine-4(3*H*)-one derivative thus obtained was converted to the corresponding 8-azapurine by treatment with $NaNO_2$ in hydrochloric acid.

VII.1.b. Method VIB

The second way of designing the [1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione system comprises the introduction of aza-group into position 5 of the uracil ring.

Matsumoto and Takahashi [175] performed condensation of *N*-(1,3-dimethyluracil-6-yl)-*S,S*-diphenylsulfylimine **202**, formed in the reaction between 6-chloro-1,3-dimethyluracil and *S,S*-diphenylsulfylimine,[176] with aryldiazonium chlorides **203** obtained *in situ*. The intermediate 5-arylazo derivatives **204** were refluxed in toluene for 1 h until the characteristic red colour disappeared. The reaction afforded the desired heterocycles **205** in high yields (Scheme 70).

Scheme 70

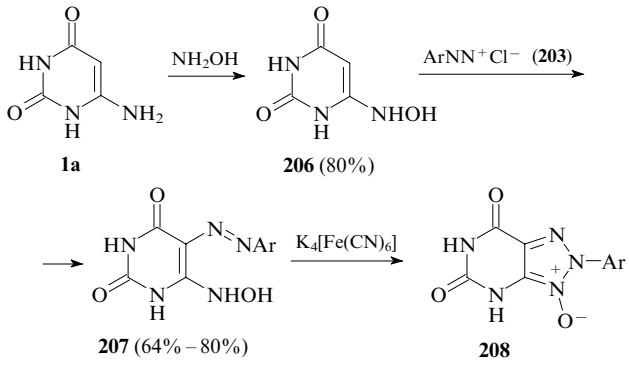


202 **204** (89% – 98%) **205** (86% – 95%)

Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$

Yavolovskii *et al.*[177] assembled the triazole ring in several steps. The original treatment of 6-aminouracil (**1a**) with hydroxylamine yielded 6-hydroxylaminouracil (**206**), which was condensed with diazonium salts **203**. 5-Phenylazo 6-hydroxylaminouracil derivative **207** obtained was oxidized with an aqueous solution of $K_4[Fe(CN)_6]$. The reaction resulted in the triazole ring closure and gave 8-aryl-8-azaxanthine 9-oxides **208** in yields of 49% – 72% in the last step (Scheme 71).

Scheme 71



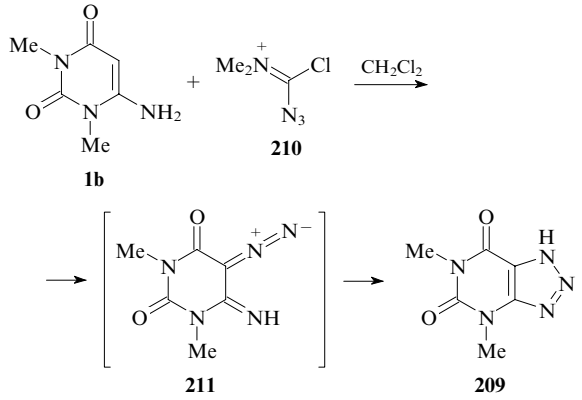
1a **206** (80%) **207** (64% – 80%) **208**

Ar = Ph, 2-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 2-HO$_2$CC$_6$H$_4$, 4-HO$_2$CC$_6$H$_4$

A synthetic procedure to obtain 8-azatheophylline (**209**) *via* the diaza group transfer has been proposed by Kokel and Boussouira.[178] This procedure involves treatment of 6-amino-1,3-dimethyluracil (**1b**) with *N,N*-dimethyl(azido)-chloromethyliminium chloride (**210**) in anhydrous dichloromethane (Scheme 72). The yield of the target compound was 65% – 68%. It is obvious that the reaction proceeds *via* the formation of intermediate **211**. This method is an

improved version of the three-step synthesis developed by Traube [179] as early as in 1900.

Scheme 72



1b **210** **211** **209**

Islam and Nagamatsu [180, 181] synthesized a series of 1,3-dialkyl derivatives of 8-phenyl-8-azaxanthines *via* oxidative cyclization of 1,3-dialkyl-6-amino-5-phenylazouracil under the action of $CuSO_4$ in boiling aqueous pyridine for 3 – 4 h in 69% – 86% yields.

Senga *et al.*[182] obtained 8-azatheophylline derivatives from 6-hydrazino-1,3-dimethyluracil **10a**. The latter was first treated with an equimolar amount of ketone in acetic acid for 2 h under reflux. This resulted in the formation of the corresponding 6-(α-methylalkylidenehydrazino)uracils **113** (50% – 87% yield), which were converted to vinyl derivatives **212** under the action of a twofold molar excess of *N*-nitrosodimethylamine and $POCl_3$ in boiling benzene. The subsequent treatment of the products with formic acid afforded 4,6-dimethyltriazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**209**) in 67% yield (Scheme 73).

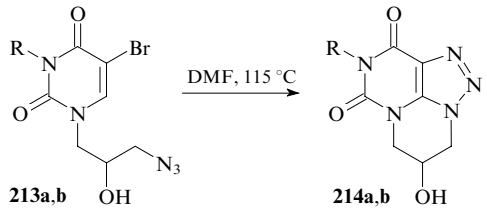
VII.1.c. Method VIC

The most advanced method to produce substituted 8-azaxanthines is intramolecular interaction of azido group with the C(5)═C(6) double bond occurring according to the addition – elimination type. Of great importance is the presence of a leaving group (Br or NO_2) in position 5 of the uracil moiety.

Jokic and Skaric [183] described intramolecular cyclization of 1-(3-azido-2-hydroxypropyl)-5-bromouracil (**213a**) proceeding in DMF at 115 °C for 16 h and yielding a tricyclic derivative of 8-azaxanthine **214a**. In such a manner, *N*-methyl analogue **214b** was obtained from compound **213b** (Scheme 74).

Under the same conditions, the *erythro*- and *threo*-isomers of 8-azaxanthines **215** in which the nitrogen atoms of the pyrimidine and triazole rings are connected by a three-carbon bridge were synthesized. However, the yields of these compounds were less than 32%.[184]

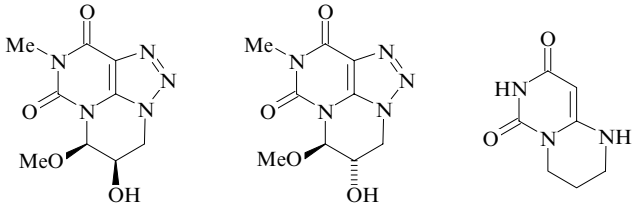
Scheme 74



213a,**b** **214a**,**b**

R = H (**a**, 70% yield), Me (**b**, 81%)

Structures 215, 216

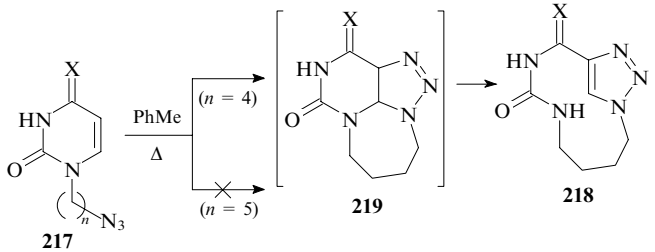


erythro-**215** *treo*-**215** **216**

Similar uracil derivatives devoid of bromine atom in position 5 do not form the 8-azaxanthine heterocyclic system. Under such conditions. they form bicyclic trimethylene derivative **216** in a high yield (91%).[185]

Intramolecular cyclization of 1-(4-azidobutyl)-substituted uracil and its 4-thio analogue (compounds **217**, $n = 4$) on heating in toluene resulted in isolation of only bicyclic derivatives **218** in yields of 80% and 74%, respectively (Scheme 75). The reaction procceds most likely *via* the formation of unstable intermediate **219**. It should be noted that 1-(5-azidopentyl)uracil **217** ($n = 5$) does not react along this route.

Scheme 75

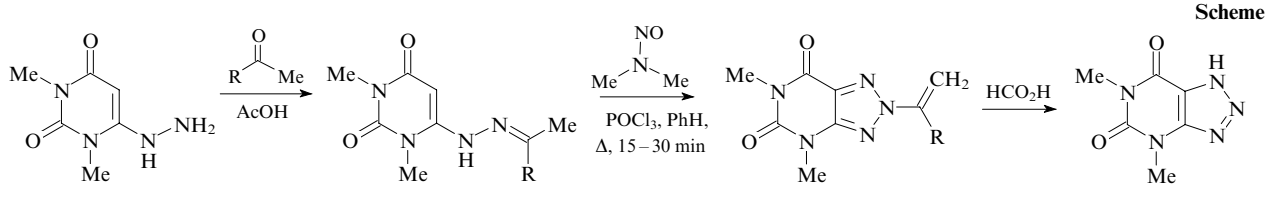


217 **219** **218**

X = O, S

Meanwhile, 1-(4-azidobutyl)-5-bromouracil (**220**) obtained by bromination of 1-(4-azidobutyl)uracil with NBS in THF at room temperature produced 3,9-tetramethylene derivative of 8-azaxanthine **221** in 49% yield on refluxing in toluene for 55 h. Obviously, the target product

Scheme 73

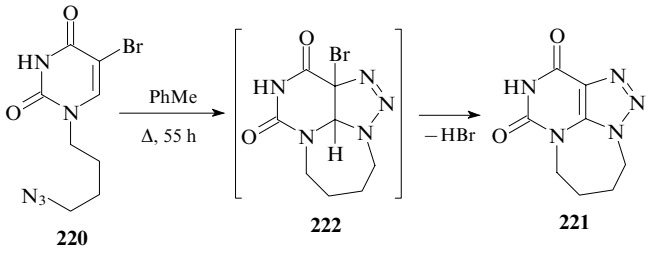


10a **113** (50% – 87%) **212** (31% – 65%) **209** (67%)

R = Me, Ph, 4-MeC_6H_4, 4-ClC_6H_4

221 was formed upon elimination of HBr from intermediate **222** (Scheme 76).

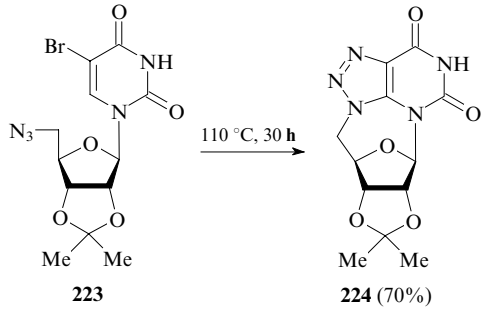
Scheme 76



220 **222** **221**

Sasaki *et al.*[186] demonstrated that 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (**223**), which is obtained in 79% yield by bromination of the corresponding uridine by NBS in THF at room temperature, can also undergo this intramolecular cyclization. On heating at 110 °C for 30 h, it is converted to 9,5′-cyclic 8-azaxanthine derivative **224** in good yield (Scheme 77).

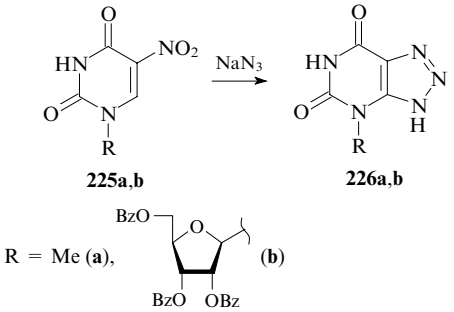
Scheme 77



223 **224** (70%)

5-Nitrouracils **225a**,**b** bearing various substituents in position 1, including Me group or the protected D-ribose residue, can form protected 1-substituted 8-azaxanthines **226a**,**b** in 81%–95% yields on heating with a large excess of sodium azide in DMF (Scheme 78).

Scheme 78

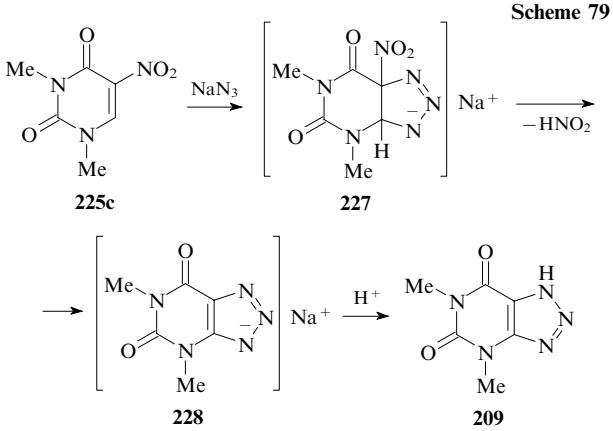


225a,**b** **226a**,**b**

3-Substituted 5-nitrouracil **225c** gave the product in this reaction in a far lower yield.[187] As in the case of 5-bromouracil, this reaction is assumed to proceed *via* the step of azide anion addition to the C(5)=C(6) double bond. Intermediate **227** eliminates a nitrous acid molecule and transforms into the desired 8-azaxanthine **209** *via* the formation of salt **228** (Scheme 79).[188]

Islam and Nagamatsu[171] described a procedure for the preparation of 8-azatheophylline comprising the condensation of 1,3-dimethyl-6-chlorouracil (**12b**) with sodium azide

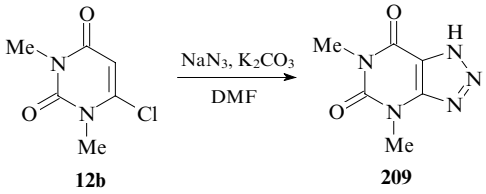
Scheme 79



225c **227** **228** **209**

in the presence of K_2CO_3 in DMF under reflux for 1.5 h. The target product **209** is formed in 67% yield (Scheme 80).

Scheme 80



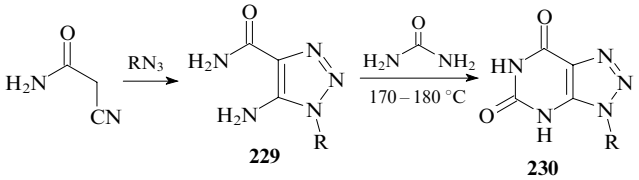
12b **209**

VII.2. Closure of a pyrimidine ring

The most convenient approach to 9-substituted 8-azaxanthines {3-substituted 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones} includes the closure of a pyrimidine ring in triazole derivatives. The starting 1-substituted triazole must bear the carboxamide (or ethoxycarbonyl) and amino group in positions 4 and 5, respectively.

Baddiley *et al.*[189] performed the condensation of cyanacetamide and methyl azide to obtain 5-amino-1-methyltriazole-4-carboxamide (**229**), which was fused with urea at 170–180 °C to afford 9-methyl-8-azaxanthine (**230a**). The authors gave no mention of the yield of the target product (Scheme 81).

Scheme 81



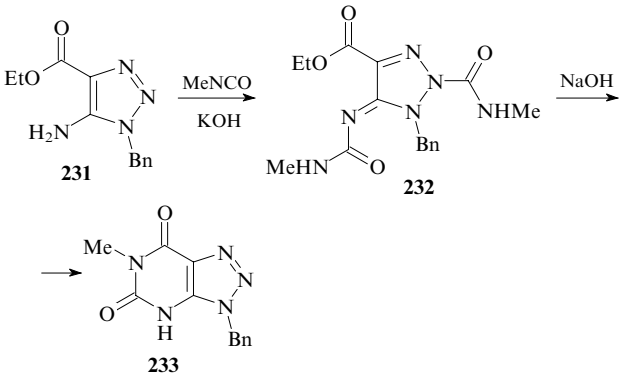
229 **230**

R = Me, Pr^i, Bn, Ph

Similarly, 9-isopropyl-, 9-benzyl- and 9-phenyl-8-azaxanthines **230** (R = Pr^i, Bn, Ph) were synthesized in 63%–83% yields.[190,191]

Treatment of ethyl 5-amino-1-benzyl-1*H*-triazole-4-carboxylate (**231**) with methyl isocyanate in $CHCl_3$ in the presence of KOH in ethanol resulted in derivative **232** (43% yield).[192] Refluxing this compound in 2 M NaOH for 4 min afforded 3-benzyl-6-methyltriazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**233**) in a quantitative yield (Scheme 82).

Scheme 82

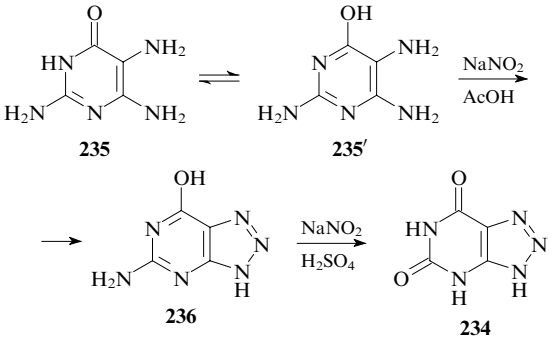


VII.3. Modification of triazole and pyrimidine rings

The direct alkylation of 8-azaxanthine (**234**) in the presence of K_2CO_3 in DMF yielded a complex mixture of N(7)-, N(8)-, N(9)-substituted (triazole moiety)[193] and N(1)-, N(3)- and OC(2)-substituted (pyrimidine moiety)[179] 8-azaxanthines.

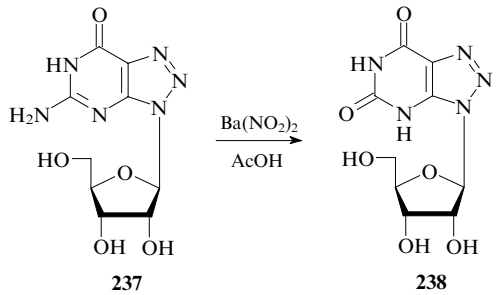
Roblin *et al.*[194] described a method for the synthesis of 8-azaxanthine **234** *via* treatment of 2,5,6-triamino-4-hydroxypyrimidine (**235′**) with sodium nitrite in acetic acid with heating for 45 min. This reaction gave initially 5-amino-7-hydroxytriazolo[4,5-*d*]pyrimidine (**236**) in 77% yield. Its subsequent reaction with sodium nitrite in 15% sulfuric acid resulted in 8-azaxanthine (**234**) in 74% yield (Scheme 83). Cavalieri *et al.*[195] synthesized 8-azaxanthine (**234**) under the same conditions, *i.e.*, deamination of 5,7-diaminotriazolo[4,5-*d*]pyrimidinium sulfate with sodium nitrite was performed in an aqueous medium.

Scheme 83



Also, deamination of 8-azaguanosine afforded a nucleoside analogue, namely, 3-β-D-ribofuranosyl-8-azaxanthine.[8] The starting nucleoside **237** was treated with barium nitrite at room temperature for 5 h in aqueous acetic acid. The yield of the 8-azaxanthine nucleoside derivative **238** was 59% (Scheme 84).

Scheme 84



Thus, despite the great variety of known synthetic methods to obtain aza and deaza analogues of xanthine, all of the approaches form two main groups: closure of a five-membered ring on the basis of a pyrimidine moiety and annulation of a pyrimidine ring to a corresponding azole. In the first group, the choice of reagents for the synthesis of the target heterocycles is rather wide, providing aza- and deazaxanthines bearing desired substituents in the five-membered moiety. Meanwhile, in the second group, the transformation is generally a condensation of amino acid derivative with (thio)urea, iso(thio)cyanate and related compounds. A wide range of biological activities of the target products comprising aza(deaza)xanthine moiety promotes intensification of the scientific research in this area. Obviously, in the nearest time, one should expect the appearance of publications dealing with the development of novel synthetic approaches to such heterocyclic systems and optimization of the known procedures.

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