HETEROCYCLIC AMIDINES AND HYDROXYAMIDINES AS SYNTHONS FOR BI- AND POLYCYCLIC HETEROCYCLES

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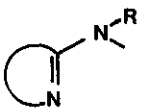
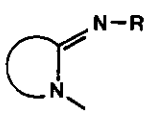
Abstract - This review summarizes the synthetic utility of heterocyclic amidines, N-hydroxyamidines and their derivatives. From these precursors a new heterocyclic ring can be formed, the cyclization involving participation of either a ring nitrogen atom or an ortho functional group.

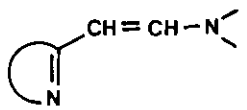
1. INTRODUCTION

The synthetic potential of enamines is well established. The related heterocyclic amidines, N-hydroxyamidines and derivatives thereof have been used recently with success for syntheses of different polycyclic heterocycles. The purpose of this review is to present the state of art in the field of heterocyclic amidines, in particular iminoamidines, and N-hydroxyamidines as synthons.

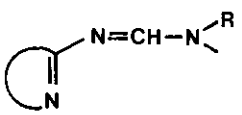
An amidine group can exist either unsubstituted or substituted at the nitrogen atom(s), but it can be also partly or completely incorporated in a heterocyclic system. The following combinations are possible (R = H, alkyl or aryl):

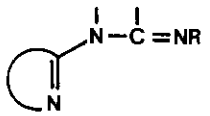


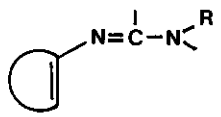




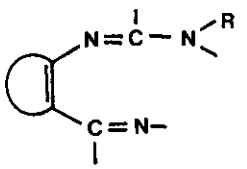
vinylogous amidine



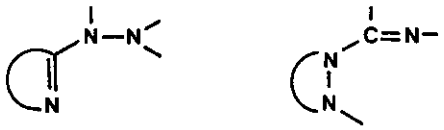




iminoamidine imidine enamidine



vinylogous iminoamidine



amidrazone

A structural variety is the N-hydroxyamidines (R = OH). Moreover, like iminium salts also amidinium salts have been used in synthesis of heterocyclic systems and their chemistry has been reviewed. [1]

Iminoamidines, having the endocyclic C-N double bond either as a part of an unsaturated or aromatic heterocyclic system, are prepared advantageously from the corresponding heterocyclic amines and various reagents with the following order of decreasing reactivity:

$HC(NR_2)_3$	>	$(R_2N)_2CHOR$	>	$R_2NCH(OR)_2$	>	$R_2NCH{=}NR$	>	$H_2NCH{=}NH$
triamino methane		aminal		amide acetal		substituted formamidine		formamidine

Mostly used are amide acetals since they show high reactivity and are also commercially available. The chemistry of formamide acetals has been reviewed.[2,3] When compared to formic acid orthoamides the following order of decreasing reactivity has been established: [4]

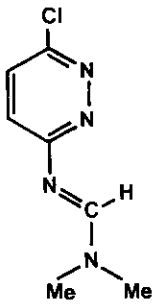
tris(dimethylamino)methane > bis(dimethylamino)-t-butoxymethane > bis(dimethylamino)ethoxymethane > bis(dimethylamino)methoxymethane > N,N-dimethylformamide di-t-butyl acetal > N,N-dimethylformamide diethyl acetal (DMFDEA) > N,N-dimethylformamide dimethyl acetal (DMFDMA).

In another, however not very efficient synthesis, the amidines were obtained from a heterocyclic azide and diethylamine or other secondary amines.[5,6] Here, the main products are the corresponding amines, but amidines result from initial cycloaddition and further decomposition of the intermediate triazolines.

As side reaction, methylation can accompany the amidine formation if DMFDMA is used as reagent. In this way, endocyclic NH groups, amino, hydroxy or mercapto groups can be methylated.[7,8] This side reaction can be eliminated if N,N-dimethylformamide dineopentyl acetal is used for amidine formation.[9] The related heterocyclic N-aminoamidines, Het-NHN=CHNMe$_2$, are also known and have been used in the syntheses of several bicyclic systems as shown later.

The free energies of the rotational barriers around the -CR-N(alkyl)$_2$ bond (R = H or Me) for a number of heteroaryl substituted formamidines and acetamidines, prepared from the correspon-

ding aminoazines and N,N-dimethylacetamide dimethyl acetal (DMADMA) have been reported.[10,11] They are in the range of 13-23 kcal/mole and structural features that influence the height of these barriers have been established. Electron donating groups which are attached to the heterocyclic ring decrease the barrier to rotation, while electron withdrawing groups increase it. The predominant forms have been determined in solution[11] and an X-ray structural determination for compound (1) has shown the following structural arrangement in solid state:[12]

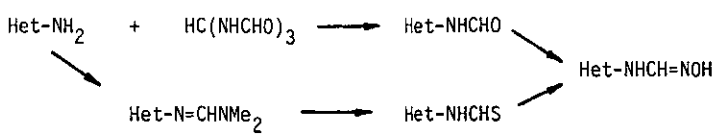


(1)

The corresponding N-hydroxyamidines of the iminoamidine series can be prepared from the iminoamidines and hydroxylamine:[13,14]

$$\text{Het-N=CHNMe}_2 \longrightarrow \underset{(2)}{\text{Het-NHCH=NOH}} \rightleftharpoons \underset{(3)}{\text{Het-NCHNHOH}}$$

These heteroaryl substituted formamidoximes (or hydroxyiminomethyleneamino heterocycles) are potential tautomeric compounds and their structure has been investigated. On hand of NMR spectra of ^{14}N and ^{15}N labelled compounds it could be established that they exist in solution exclusively in the hydroxyimino form (2) and not in the hydroxylamino form (3).[15] In another synthetic approach they can be prepared from the corresponding aminoazines with trisformamidomethane and the obtained formylamino heterocycles are treated subsequently with hydroxylamine.[16] It is also possible to transform some amidines first into the corresponding thioformylamino compounds with hydrogen sulfide and with hydroxylamine the desired functionality is formed.[17]

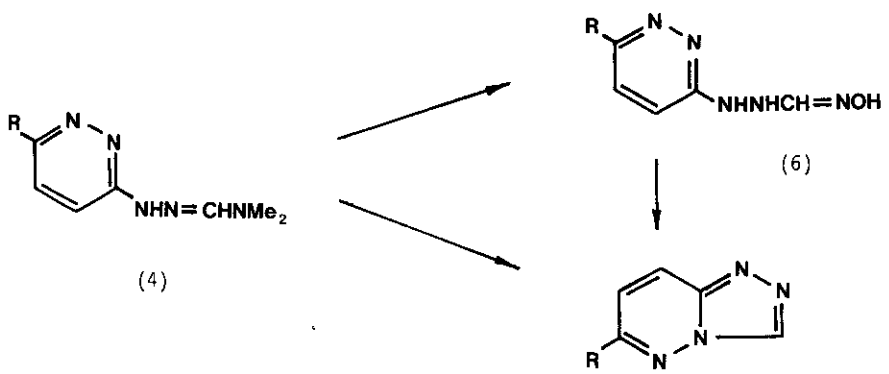


Other special cases of amidine or N-hydroxyamidine formation are represented by ring opening reactions and are presented later in this article.

2. CYCLIZATION TO HETEROCYCLES WITH RING NITROGEN PARTICIPATION

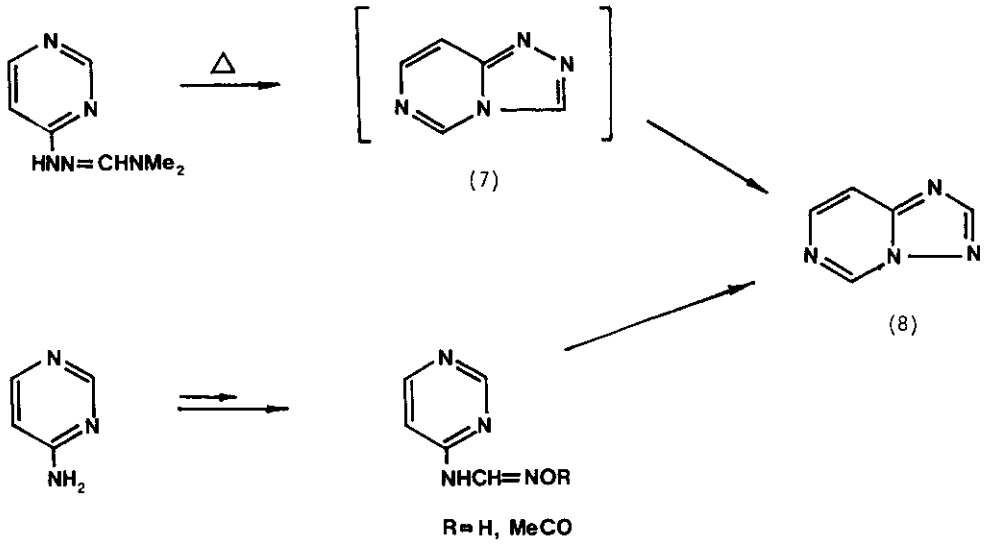
Two general synthetic approaches have been so far elaborated. In the first one a heterocyclic hydrazino compound is treated with DMFDMA and subsequent cyclization gives a fused triazolo heterocycle. The second synthetic possibility leads to the corresponding fused triazolo heterocycles or their 3-oxides and as synthons the corresponding N-hydroxyamidines are used.

Contrary to heterocyclic amidines the related aminoamidines are thermally less stable. For example, compound (4) easily cyclized to (5), which is obtainable also by thermal cyclization of the corresponding N-hydroxyimino compound (6).[18]



(4) (6) (5)

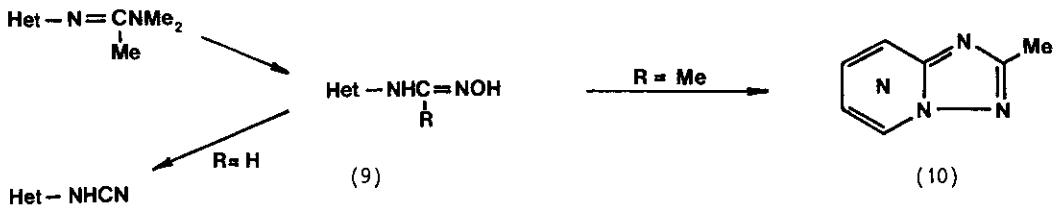
Cyclization of an N-aminoamidine side chain as in the above example is anticipated to give a fused triazolo ring with a 1,2,4-nitrogen arrangement in the five-membered ring. However, this is not always the case. It is well known that the Dimroth type rearrangements of triazoloazines are possible to give the thermodynamically more stable 1,3,4-nitrogen arrangement in the five-membered ring.[19] When starting from 4-hydrazinopyrimidine and following the usual transformation sequence with DMFDMA and thermal cyclization, it was anticipated that the product should have the s-triazolo(4,3-a)pyrimidine structure (7). However, it could be established that during the synthesis rearrangement took place and the product was actually s-triazolo(1,5-a)pyrimidine (8). This bicycle could be also prepared in a similar reaction sequence from 4-aminopyrimidine via the N-hydroxy- and N-acetoxyamidine.[20]



The last mentioned synthetic sequence has proven to be a versatile synthetic route to various triazoloazines. The cyclization step can involve either treatment of the N-hydroxyamidine with polyphosphoric acid or acetylation with subsequent thermal cyclization. The following bicyclic systems and derivatives thereof have been prepared by this method:[14] s-triazolo(1,5-a)-pyridine,[13,14] s-triazolo(1,5-b)pyridazine,[13,14,21] s-triazolo(1,5-a)pyrimidine,[13,14,21] s-triazolo(1,5-a)pyrazine,[13,14,21] s-triazolo(1,5-a)-1,3,5-triazine,[13,14] and s-triazolo-(1,5-b)-1,2,4-triazine.[21] This synthetic principle could be applied also for the preparation of more complex tricyclic systems like imidazo(2,1-f)-s-triazolo(2,3-b)pyridazine,[18] s-triazolo-(4,3-b)-s-triazolo(5,1-f)pyridazine,[18] pyrido(3,2-d)-s-triazolo(1,5-b)pyridazine,[14] pyrido-(2,3-d)-s-triazolo(1,5-b)pyridazine,[14] bis-s-triazolo(1,5-b:5',1'-f)pyridazine,[14] s-triazolo-(5,1-b)pteridine,[22] and s-triazolo(5,1-c)tetrazolo(1,5-a)pyrazine.[23] The same reaction sequence, when applied to 4-aminopteridine, was successful only until the preparation of 4-(acetoxyimino-methyleneamino)pteridine and the attempted ring closure yielded 4-cyanoaminopteridine.[24] In similar manner, adenine couldn't be transformed into the tricyclic system.[25]

Hydroxyiminomethyleneamino heterocycles or their C-methyl derivatives (N-hydroxyacetamidines or hydroxyiminoethyleneamino heterocycles) are usually dehydrated under the influence of DMFDMA, phosphorus oxychloride and other reagents to give the corresponding cyanoamino heterocycles.[21,26] On the other hand, N-heteroarylacetamide oximes (9, R = Me), prepared from the corresponding N,N-dimethyl-N'-heteroarylacetamidines, cannot eliminate water from the oxime group and after

treatment with polyphosphoric acid or phosphorus oxychloride they are cyclized to 2-methyl-s-triazolo(1,5-x)azines.[21]



(9) (10)

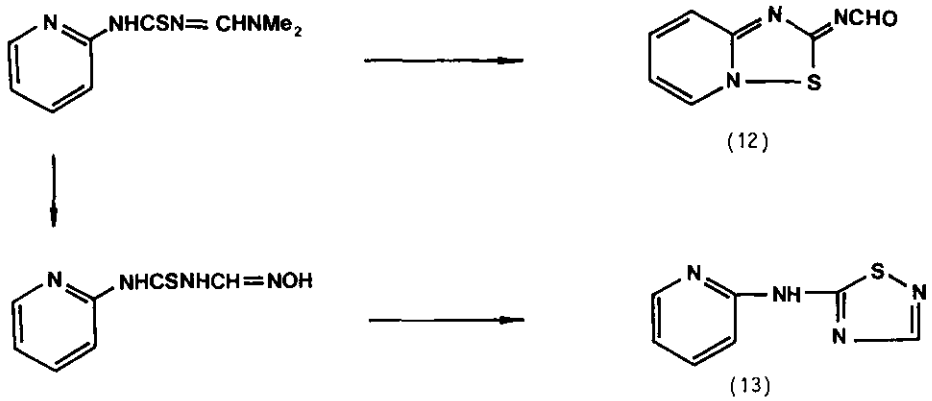
In this manner derivatives of 2-methyl substituted s-triazolo-(1,5-b)pyridazine, -(1,5-a)pyrimidine, -(1,5-a)pyrazine and -(1,5-b)-1,2,4-triazine have been prepared.[21]

In a modified synthetic approach the corresponding amidines were treated with hydroxylamine O-sulfonic acid and by this direct synthesis s-triazolo(1,5-a)pyridines and s-triazolo(5,1-a)-isoquinoline have been prepared.[27] It is anticipated that the reaction proceeds by replacement of the dimethylaminc group in the corresponding amidine with hydroxylamine O-sulfonic acid, followed by cyclization.

Another variant of this synthetic principle involves oxidative cyclization of hydroxyimino-methyleneamino heterocycles. In the presence of an oxidizing agent like N-bromosuccinimide or bromine in glacial acetic acid the corresponding 3-oxides of substituted s-triazolo(1,5-a)pyrazine, -(1,5-a)pyridine and -(1,5-b)pyridazine (11) were obtained.[28,29]

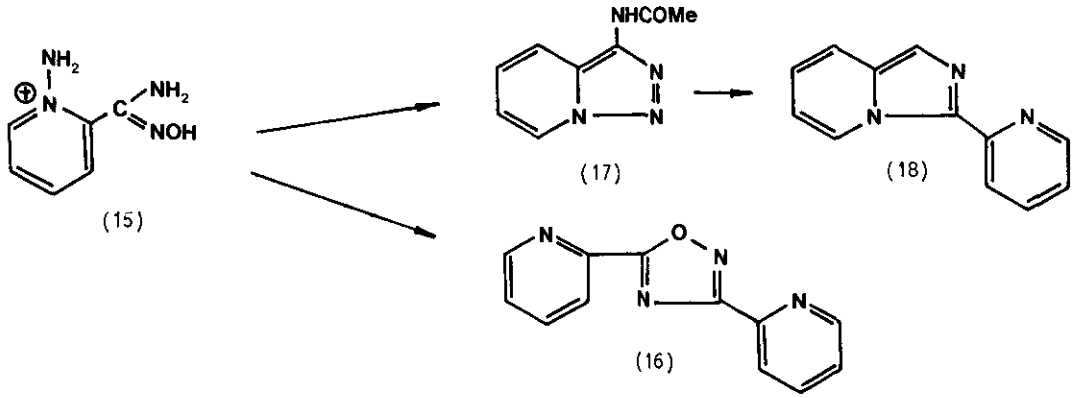
(11)

An amidine side chain, formed from a thioureido group can also participate in new ring formation. The reaction product between N-(pyridyl-2)thiourea and DMFDMA can be transformed by oxidative cyclization into a 1,2,4-thiadiazolo(2,3-a)pyridine derivative (12). On the other hand, transformation with hydroxylamine yielded the N-hydroxyamidine and this can be thermally converted into the substituted thiadiazole (13).[30]

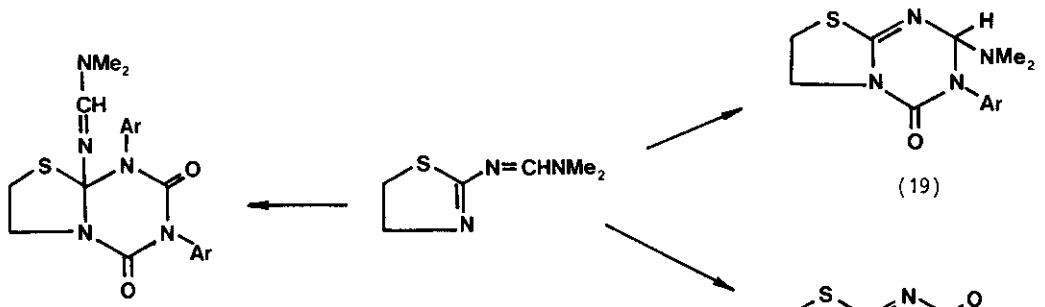


Heterocycles with a hydroxyimino group at position ortho to the ring nitrogen can also be regarded as structural equivalents to the hydroxyiminomethyleneamino compounds. For example, 1-amino-2-hydroxyimino-1,2-dihydropyridine reacted either with DMFDMA or with formic acid or trifluoroacetic anhydride to give s-triazolo(1,5-a)pyridine 1-oxide and its 2-trifluoromethyl derivative, respectively (14).[31,32]

On the other hand, the amidoxime (15) is transformed upon heating into 3,5-bis(pyridyl-2')-1,2,4-oxadiazole (16), whereas in acetic anhydride at room temperature 1-acetylamino-v-triazolo(1,5-a)-pyridine (17) is formed. The latter compound can be rearranged into 3-(pyridyl-2')imidazo(1,5-a)-pyridine (18).[31]



Heterocyclic compounds with an amidine side chain undergo also cycloadditions. The reaction with isocyanates gives different adducts, depending on the reaction conditions and substituents present on the heterodienes.[33] For example, a |2+4| cycloadduct (19) is formed at room temperature, but with excess of the isocyanate at 180°C a 1:2 cycloadduct (20) is formed, involving the reaction at the endocyclic imine bond. At still higher temperatures (240-250°C) adducts of the type (21) are formed.



(19)

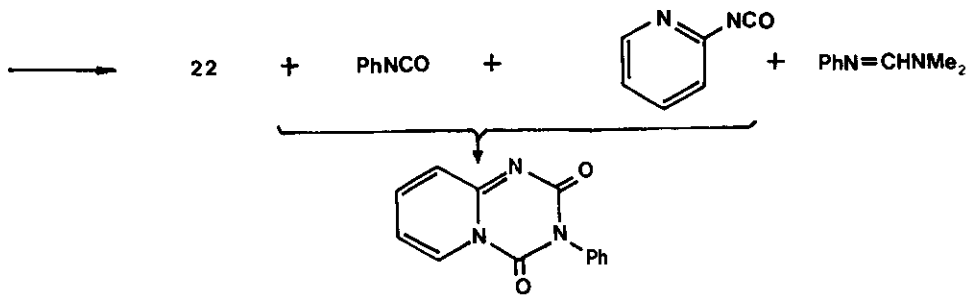
(20)

(21)

The formamidine, prepared from 3-aminopyridazine or its 6-chloro analog and DMFDMA, when heated in the presence of phenyl isocyanate, is transformed into a derivative of pyridazino(2,3-a)-1,3,5-triazine-2,4-dione.[34] Later, it was found that if the reaction mixture was allowed to stand at room temperature, from the amidine (22) a |2+2| cycloadduct (23) is formed first. At higher temperatures cycloreversion takes place in two different ways to give two different amidines and two different isocyanates. Now, both isocyanates undergo a |2+4| cycloaddition to form the fused triazine derivative (24).[35]

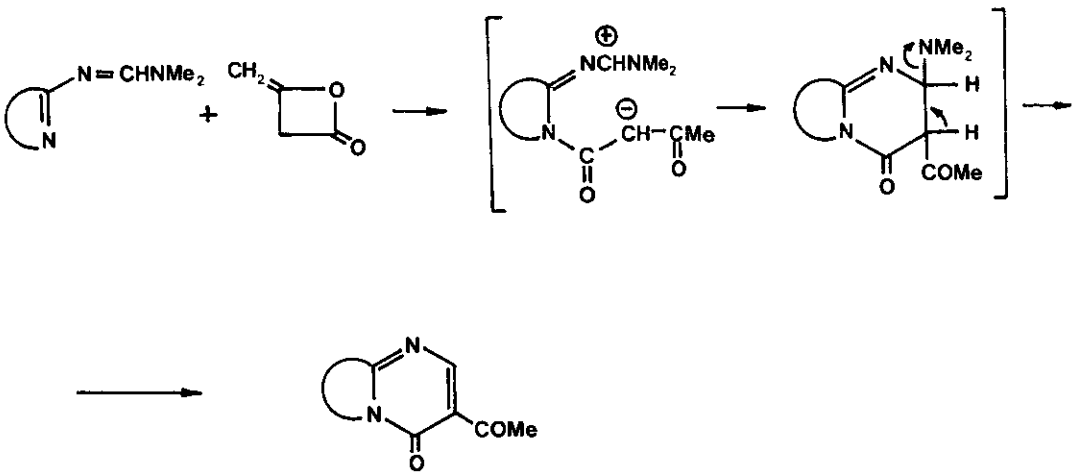
(22)

(23)



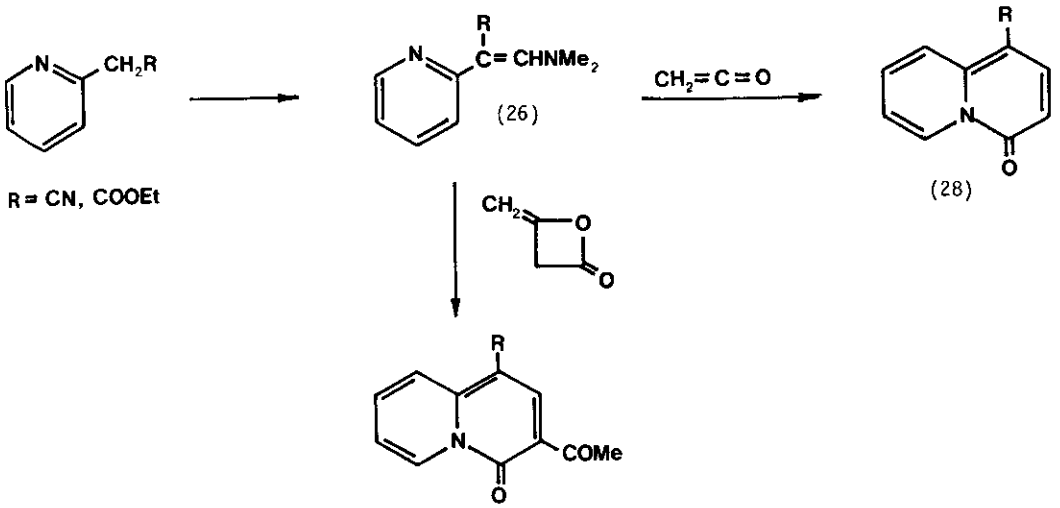
(24)

Heterocyclic amidines form cycloadducts also with diketene and heterocyclic systems with a fused pyrimidinone ring (25) are formed.[36] The 1,4-dipolar cycloaddition is postulated to proceed as an electrophilic addition of the carbonyl carbon of diketene to the heterocyclic ring nitrogen and the dipolar intermediate is subsequently cyclized with elimination of dimethylamine.



(25)

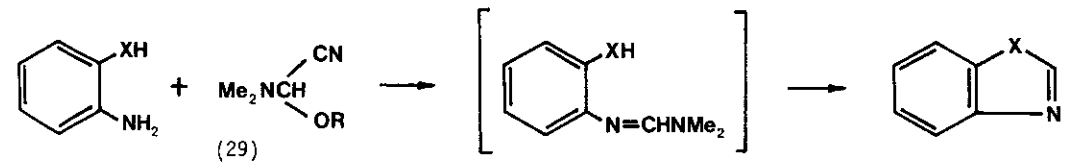
The reaction has been successfully extended to various five- and six-membered heteroaromatics and their benzo analogs. Vinylogous amidines in the pyridine (26) or quinoline series, prepared from the corresponding heteroaryl acetonitriles or acetates, react with ketene or diketene to give the corresponding quinolizine derivatives (27 and 28) or their benzo analogs.[37]



3. CYCLIZATION TO HETEROCYCLES WITH PARTICIPATION OF A NEIGHBORING FUNCTIONAL GROUP

There are many examples of heterocyclic ring formation from heterocyclic amidines with participation of an ortho functional group like amino, hydroxy, mercapto, carboxamido, cyano, amidoxime, ethoxycarbonyl, etc.

In a similar way as N,N-dimethylformamide dialkyl acetals the corresponding (dimethylamino)-alkoxyacetonitriles (29) also react with primary amines to give the corresponding amidines. During the reaction a molecule of alcohol and HCN are eliminated. From o-difunctional benzenes, like o-phenylenediamine or o-aminophenol, benzimidazole or benzoxazole (30) were obtained.The intermediate amidines were not isolated and the reagent serves actually as one carbon synthon.[38]

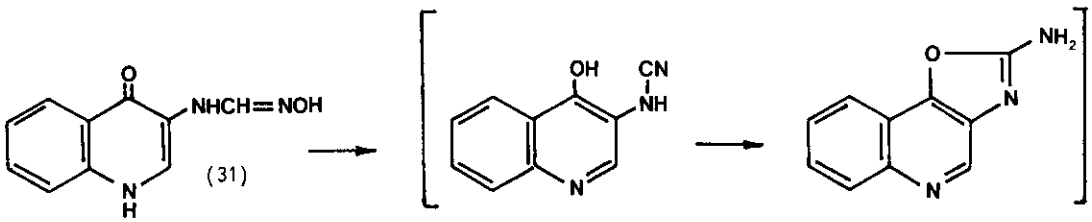


(30)

Other difunctional azines have been cyclized with DMFDMA at temperatures over 100°C. In this manner benzimidazole, benzothiazole, thiazolo(5,4-b)pyridine, imidazo(4,5-b)pyridine, imidazo-(4,5-c)pyridine, pyrido(3,2-d)pyrimidin-4(3H)-one and pyrido(2,3-d)pyrimidin-4(3H)-one have been prepared.[39] From 2,4,5-triaminopyrimidine and DMFDMA, however, only the triamidine was obtained. This, after being heated in diethylene glycol, cyclized to the corresponding purine.[25] Cyclization,

accompanied with simultaneous chlorine displacement, occurred more readily with 2-chloro-4,5-diaminopyrimidine to give 2-dimethylaminopurine. [25]

A particular case represents the formation of a fused oxazolo ring from o-amino-oxo (or hydroxy)-heterocycles. For example, compound 31 when treated with DMFDMA is transformed into the tricyclic derivative (32). The reaction proceeds via the intermediate cyanoamino compound, DMFDMA acting in this step as a dehydration agent.[40]



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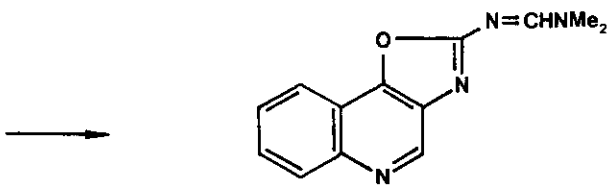
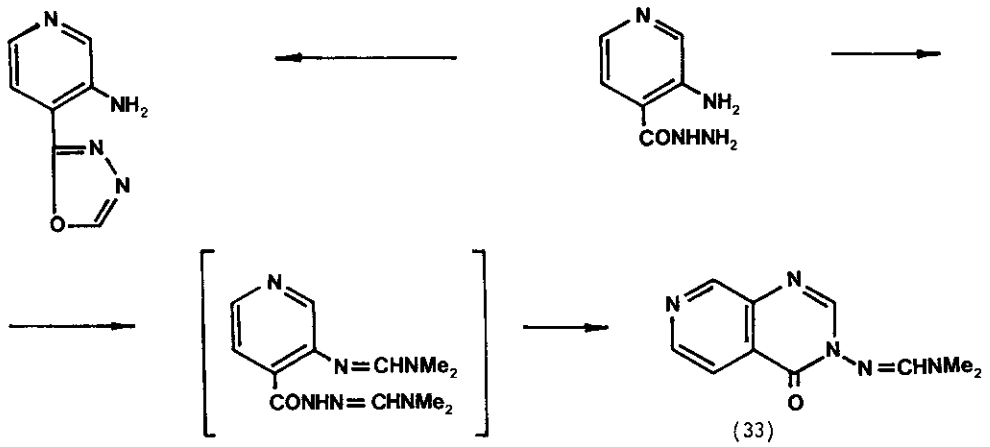


(32)

A similar reaction sequence, when applied to 2-amino-3-hydroxypyridine afforded the corresponding oxazolo(4,5-b)pyridine and likewise the oxazolo(5,4-d)pyrimidine system was formed.[23]

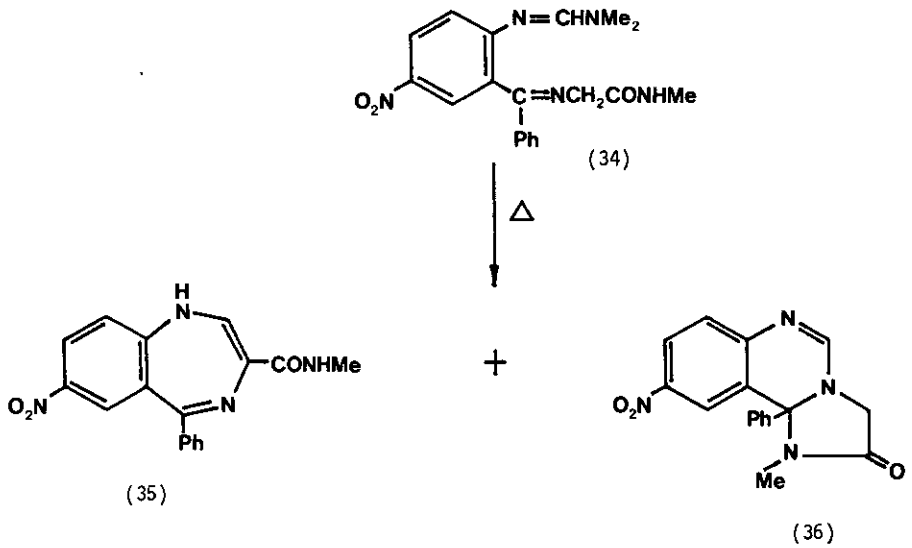
There are several examples of participation of carboxamido or modified carboxyl group in the cyclization step with an amidine side chain. In this way, pteridin-4-ones could be prepared from 2-amino-3-pyrazinecarboxamides and DMFDEA, [41] whereas from 2-substituted 6-aminopyrimidine-5-carboxamides the corresponding pyrimido(4,5-d)pyrimidin-4-ones were obtained.[23,42]

When hydrazides of o-aminoarylcarboxylic acids are treated with DMFDMA a 1,3,4-oxadiazole ring is formed. This is also the case with some aminopyridinecarbohydrazides, but eventually bicyclic products are formed. In this way some pyrido(3,4-d)pyrimidines (33)[43] and pyrimido(4,5-d)pyrimidin-4-ones [23] have been prepared.



(33)

Some amidines have been used in the synthesis of 1,4-benzodiazepines. For example, the amidine (34) was converted thermally into the corresponding 1,4-benzodiazepine (35) as the main product, the tricyclic compound (36) being also formed.[44]



(34)

(35)

(36)

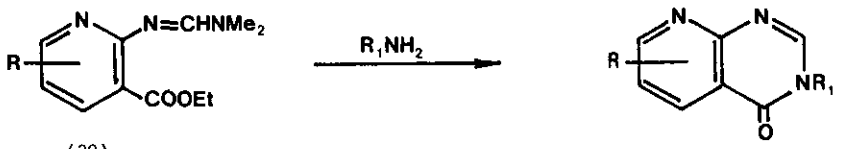
It appears that in the formation of the first product (35) the methylene group is involved in ring formation, whereas in the case of the second product (36) the imine nitrogen (or the tautomeric form) in the amide side chain participates in the pyrimidine ring formation. Thereafter, the residual side chain is involved in the five-membered ring formation.

The pyrido(2,3-d)pyrimidine ring system has been obtained from a pyrimidine precursor by forming first the amidine (37) with N,N-dimethylacetamide diethyl acetal (DMADEA). Under basic

conditions an ortho ethoxycarbonyl group is condensed with methyl group to form thus the pyridine part of the bicycle (38).[45]

(37) (38)

It is also possible to prepare the same bicyclic system from the appropriate pyridine (39) and an arylalkylamine.[46]

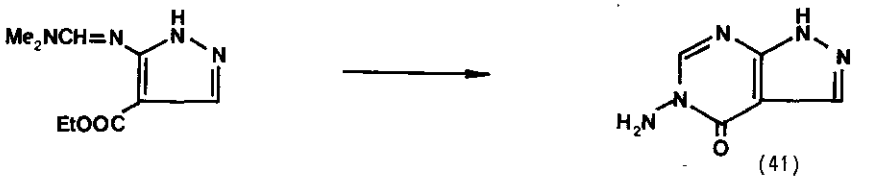


(39)

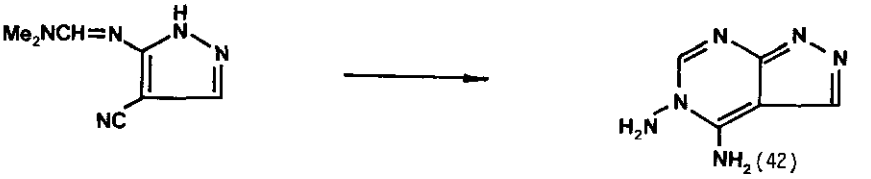
Similarly, 1-substituted or unsubstituted ethyl 5-aminopyrazole-4-carboxylates react, after being transformed into amidines, with arylalkylamines at about 180°C to form the corresponding pyrazolo-(3,4-d)pyrimidines (40).[46,47]

(40)

Heterocyclization is possible also through another approach. The amidine, prepared from 3-amino-pyrazole-4-carboxylate, reacted at room temperature with hydrazine to give the pyrazolo(3,4-d)-pyrimidine derivative (41) from which upon deamination allopurinol was obtained.[25] A similar reaction sequence, when applied to 3-amino-4-cyanopyrazole, gave the same bicyclic system (42).[25]



(41)



(42)

An ortho cyano group can participate in ring formation if the corresponding amidine is treated with hydrogen sulfide under alkaline conditions. For example, pyrido(2,3-d)pyrimidine-4(3H)-thione (43) could be prepared from 2-amino-3-cyanopyridine in this manner.[17]

(43)

An uncommon way was used to prepare an amidine (44), which was obtained from an amide and diethyl acetal of tetramethylurea. Compound (44), when heated at 200-205°C, cyclized to the pyrrolo(3,2-c)-pyridine (45, R = NMe_2).[48] If the amidine was prepared with DMFDMA (46) a similar bicyclic product (45, R = H) was obtained.[49]

(44)

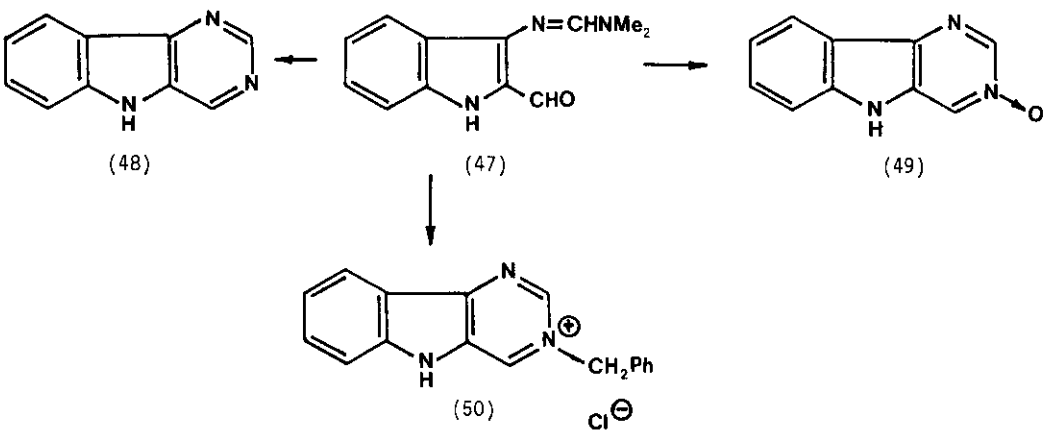
(45)

R = NMe_2, H

(46)

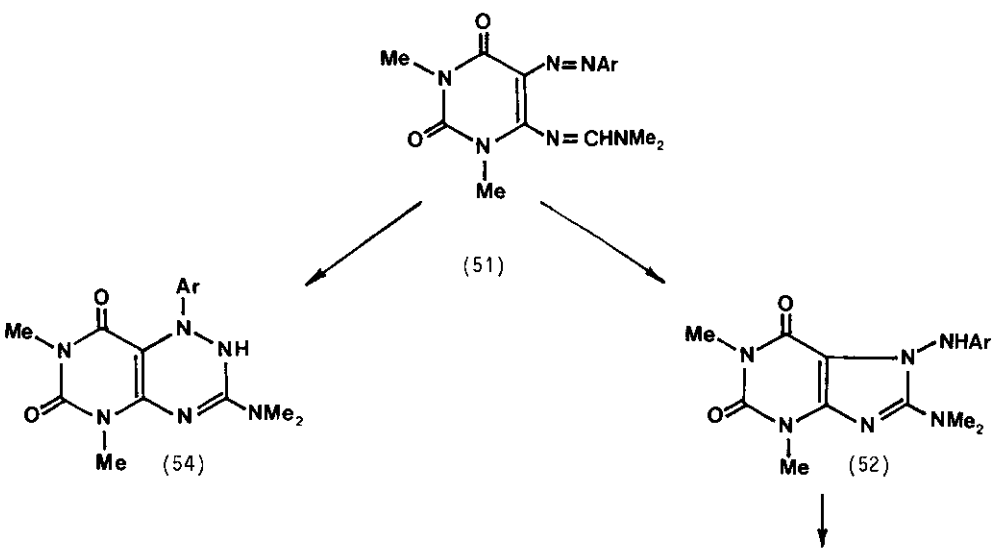
Starting from the corresponding analogs with a six- or seven-membered ring analogous bicyclic compounds were prepared.[50]

2-Formylindolylformamidine (47), prepared from 3-aminoindole by the Vilsmeier reaction, could be transformed either with aqueous ammonia, or with hydroxylamine or with benzylamine into the corresponding pyrimido(5,4-b)indoles (48, 49, 50).[51]

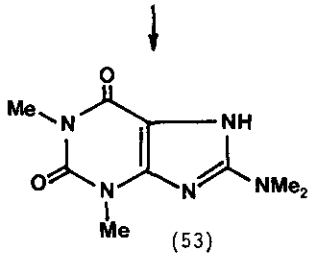


(48) (47) (49) (50)

From certain 6-aminopyrimidines purines and pyrazolo(3,4-d)pyrimidines can be synthesized by the action of DMFDMA. The amidines (51), prepared from 6-amino-1,3-dimethyl-5-arylazouracils and DMFDMA, are transformed upon heating at 210-220°C into a mixture of 8-dimethylaminotheophiline (53) and pyrimido(4,5-e)-1,2,4-triazines (54). The purine derivative is formed from the intermediate (52) which could be isolated from the initial reaction mixture.[52]



(51) (54) (52)



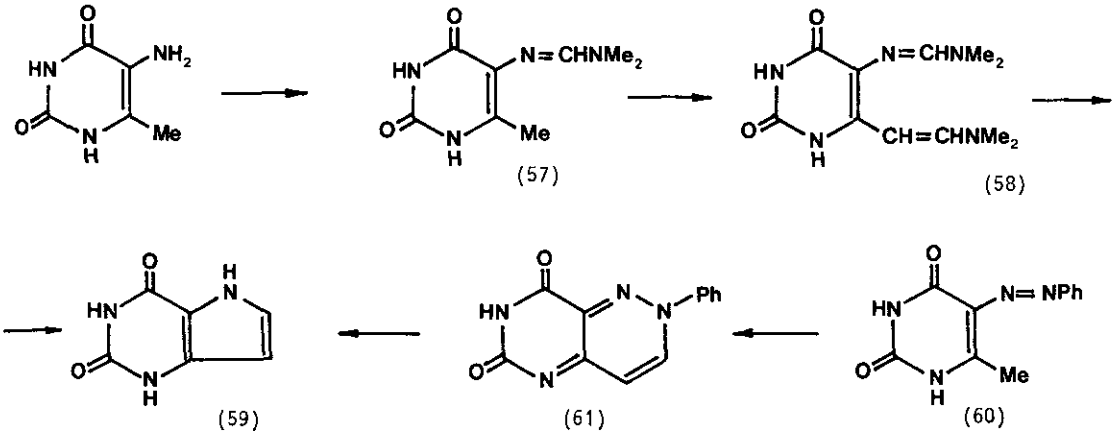
(53)

In a similar manner, amidines of 5-arylidene uracils (55) are transformed upon heating in sulfolane into the corresponding 6-arylpteridines (56).[53,54]

(55) (56)

The reaction is interpreted as 1,6-coupling, whereas photolysis of the starting amidines gave theophylline as a result of 1,5-coupling reaction.[54] On the other hand, a very facile cyclization to 8-dimethylaminopurines takes place when 6-amino-5-nitrosopyrimidines are treated with DMFDEA at $0^{o}C$ to room temperature.[55]

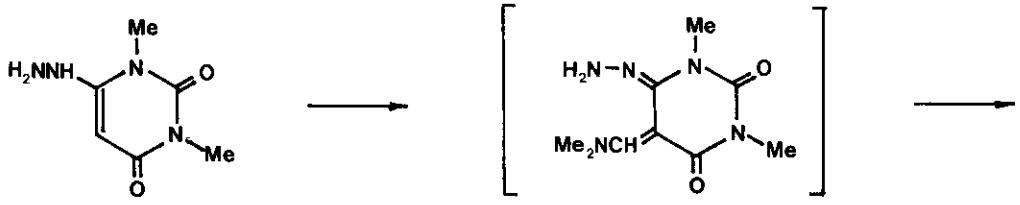
5-Amino-6-methyluracil was transformed with t-butoxybis(dimethylamino)methane, an aminal, at room temperature, into the amidine (57), whereas at elevated temperature also the methyl group underwent transformation to give compound (58). The latter was transformed with ammonia at room temperature into the pyrrolo(3,2-d)pyrimidine derivative (59).[56]



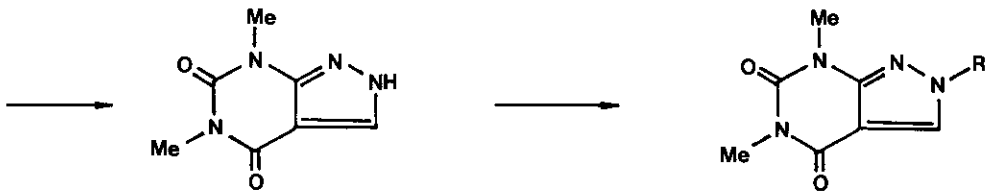
(57) (58) (59) (60) (61)

This bicyclic system could be obtained also from the azopyrimidine (60) after treatment with the above mentioned aminal and subsequent hydrogenation of the obtained pyrimido(5,4-c)pyridazine (61).

2-Alkylpyrazolo(3,4-d)pyrimidines have been prepared from the corresponding dimethylformamide dialkyl acetals and 1,3-dimethyl-6-hydrazinouracil at 150°C.[57] The reaction is interpreted as to proceed not at the hydrazino group but first at position 5 to give the 5-dimethylaminomethylene derivative (62). After elimination of dimethylamine the bicyclic product (63) is formed and after alkylation the corresponding 2-alkyl derivatives (64) are obtained. At 90°C the starting uracil is transformed to the non-alkylated product (63), but at 150°C with DMFDMA the 2-methyl derivative is obtained.

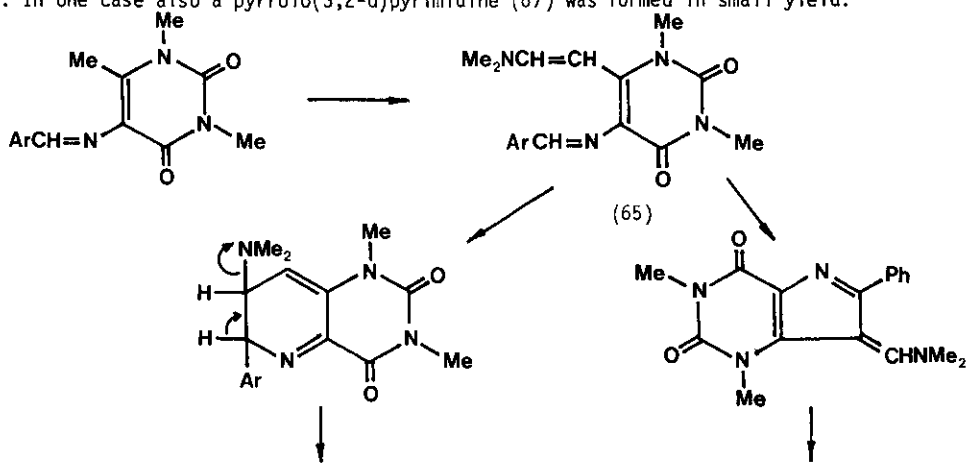


(62)

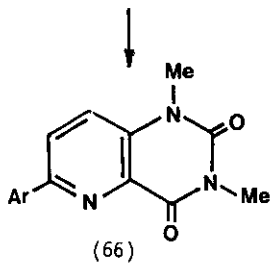


(63) (64)

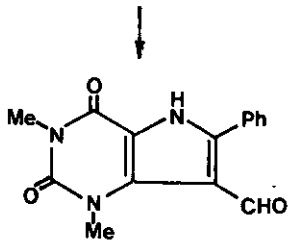
The reaction between 5-arylideneamino-1,3,6-trimethyluracils and DMFDMA at 130°C afforded as main products the corresponding pyrido(3,2-d)pyrimidines (66) together with 6-dimethylaminovinyluracils (65). In one case also a pyrrolo(3,2-d)pyrimidine (67) was formed in small yield.[58]



(65)

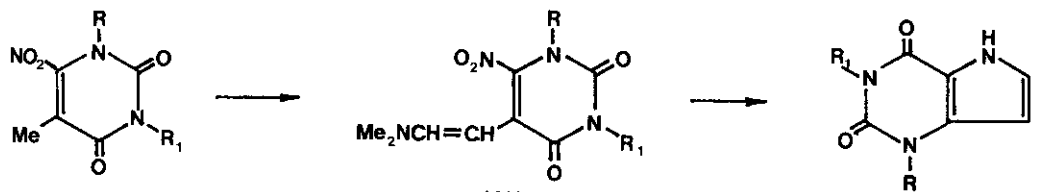


(66)



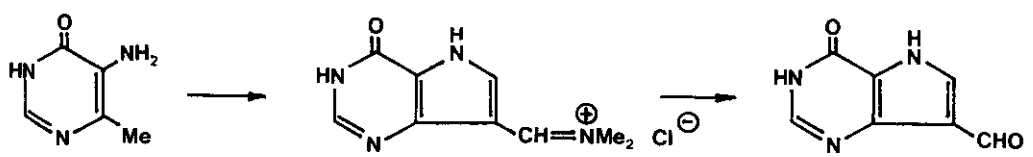
(67)

The formation of these bicyclic products is explained either in terms of a 1,6-cycloaddition (the formation of the pyridopyrimidine) or a 1,5-cycloaddition (the formation of the pyrrolopyrimidine) from the dimethylaminovinyluracil (65). Several bicyclic heterocycles have been prepared from vinylogous amidines. A general synthetic approach involves the reaction between an activated methyl group (ortho or para to the ring nitrogen) with an amide acetal and followed by cyclization to an ortho amino group, usually generated in situ. For example, 6-methyl-5-nitrouracils when treated with DMFDMA were transformed into the corresponding 6-(dimethylaminovinyl)-5-nitrouracils (68). Catalytic reduction of the nitro group caused simultaneous formation of the corresponding pyrrolo(3,2-d)pyrimidines (69).[59]



(68) (69)

Similarly, 5-amino-6-methylpyrimidin-4(3H)-one yielded under the conditions of the Vilsmeier reaction the pyrrolo(3,2-d)pyrimidine derivative (70).[60]

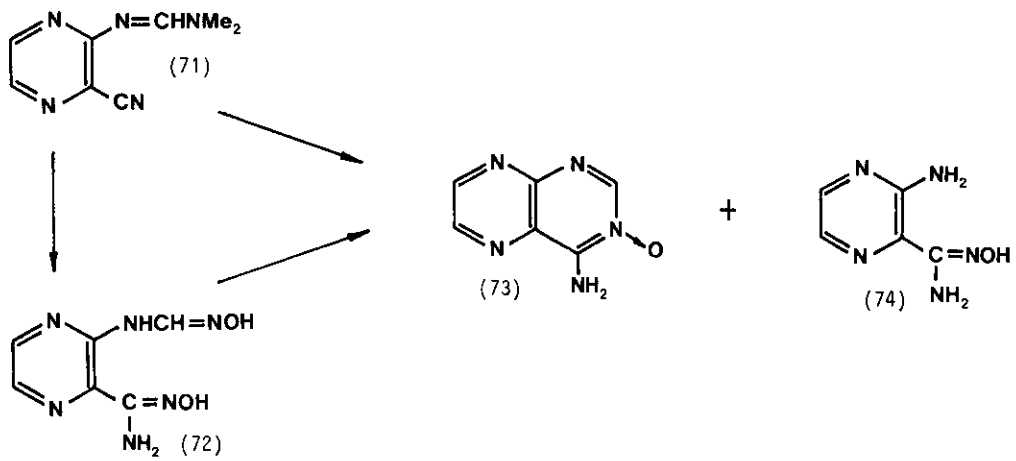


(70)

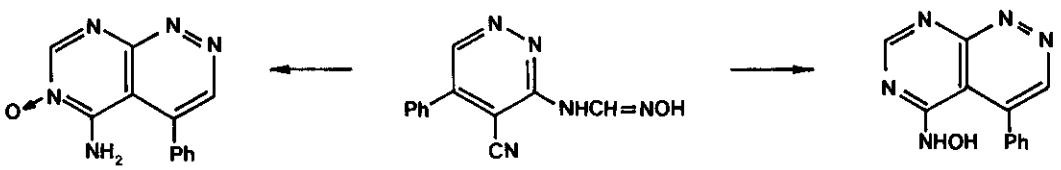
As an extension of the above synthetic principle, from 2-methyl-3-nitropyridines the corresponding pyrrolo(3,2-b)pyridines were prepared[61] and 4-methyl-3-nitropyridines were transformed into pyrrolo(2,3-c)pyridines.[62,63]

On the other hand, some interesting transformations have been observed with heterocyclic

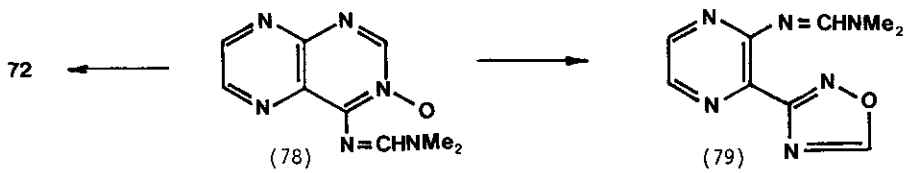
o-cyanoaminoazines. 2-Amino-3-cyanopyrazine afforded with DMFDMA the amidine (71) and this was converted with free hydroxylamine at $0^{o}C$ into the amidoxime (72). The latter is transformed upon heating into the corresponding pteridine 3-oxide (73).[64] However, if hydroxylamine hydrochloride was used, upon heating a mixture of products was obtained, the N-oxide (73) being the main product, accompanied with the amidoxime (74), 2-amino-3-cyanopyrazine and 2-amino-3-pyrazinecarboxamide as minor components.[8]



In a similar manner from the corresponding pyridazine (75) the pyrimido(4,5-c)pyridazine system (76) was obtained in boiling ethanol.[23] In boiling water the amidoxime (75) yielded the 5-hydroxyamino bicycle (77).

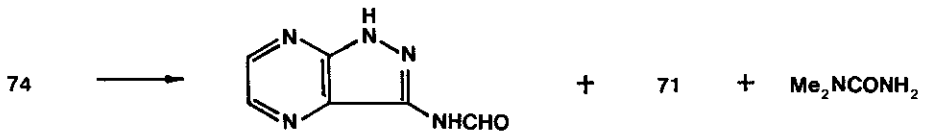


If 4-aminopteridine 3-oxide (73) was transformed with DMFDMA into the amidine (78), the attempted transformation into the N-hydroxyamidine with hydroxylamine caused ring opening with simultaneous formation of a amidoxime and hydroxyiminomethyleneamino functions (72).[65] On the other hand, the reaction with dimethylamine hydrochloride afforded the corresponding amidine (79), the reaction involving again the ring opening of the pyrimidine part.[65]



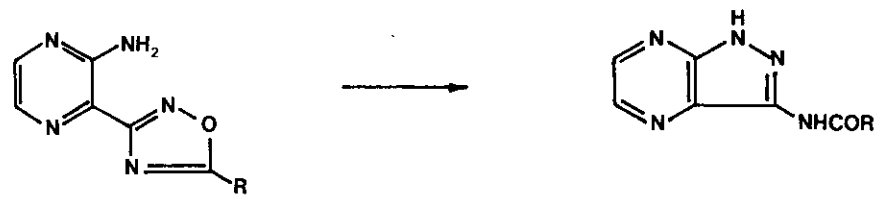
(78) (79)

Amidoximes, prepared from o-aminocyanoazines, revealed an interesting reactivity when treated with formamide acetals. For example, the amidoxime (74) when heated in the presence of DMFDMA in toluene afforded a mixture of the corresponding pyrazolo(3,4-b)pyrazine (80), the formamidine (71) and N,N-dimethylurea.[66,67] Yield of the particular product depends on the quantity of the reagent used.



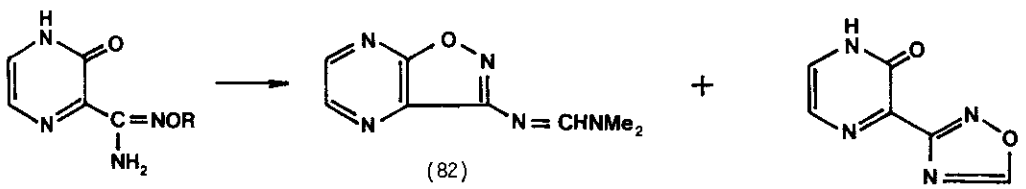
(80)

The pyrazolo(3,4-b)pyrazine system is obtainable also from the corresponding oxadiazolyl derivatives (81) after treatment with DMFDMA.[66,67]



R= Me , Ph (81) R = Me , Ph

In a similar manner also the isoxazolo(4,5-b)pyrazine system (82) can be formed from the corresponding oxo compound.[66,67]

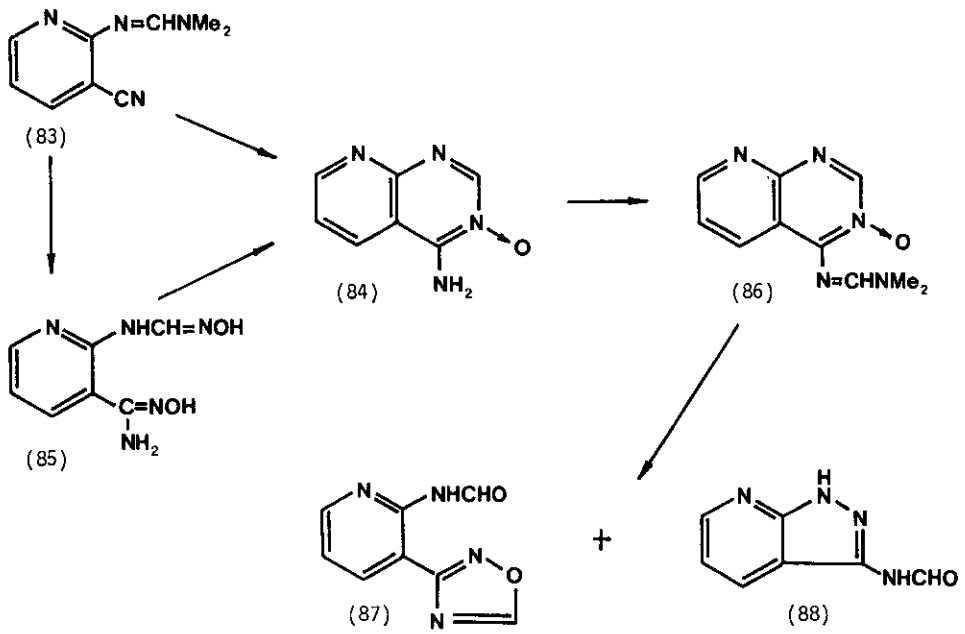


(82)

R = H, COMe

Depending on the reaction conditions only the bicyclic product or a mixture of this and the oxadiazolyl derivative was obtained. Evidently, in all these cases an intermediate amidine is formed. These reactions have been extended also to the thioxo analogs and from 3-cyanopyrazine-2(1H)-thione the isothiazolo(4,5-b)pyrazine system was obtained,[23] whereas from 3-cyanopyridine-2(1H)-thione 3-aminoisothiazolo(5,4-b)pyridine was prepared.[67] A general mechanism for these transformations has been proposed.[67]

Similar transformations have been performed also in the pyridine series. The amidine (83), when treated with a methanolic solution of hydroxylamine hydrochloride was, however, not transformed into the anticipated N-hydroxyamidine, but 4-aminopyrido(2,3-d)pyrimidine 3-oxide (84) was obtained straightforward.[68,69] With free hydroxylamine the amidoxime (85) was formed and this could be transformed either thermally or in the presence of polyphosphoric acid into the cyclic product (84). Further preparation of the amidine (86) and its transformations are interesting. It was decomposed hydrolytically at room temperature into the oxadiazolyl derivative (87) as the main product, accompanied with a small amount of the pyrazolo(3,4-b)pyridine derivative (88).[68,69]



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