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Heterocyclisation of trisubstituted formamidines containing an aryl or hetaryl substituent at the imine nitrogen atom

G V Oshovsky, A M Pinchuk

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Abstract. Published data on the cyclisation of N^1,N^1-disubstituted N^2-aryl- and N^2-hetaryl-formamidines are analysed, described systematically and generalised. The bibliography includes 147 references.

I. Introduction

Heterocyclisations play an important role in organic chemistry and provide key, sometimes irreplaceable, approaches to the preparation of heterocyclic systems. Since heterocyclic derivatives represent the most numerous class of organic compounds covering about two-thirds of all natural and synthetic products, it is important to describe systematically the methods used to prepare them. At present, the syntheses of heterocyclic compounds are classified using three different approaches: in terms of the cyclisation product (heterocyclic compound or a class of compounds), in terms of the type of ring-forming reaction, and in terms of the functional groups or classes of organic compounds involved in the construction of the heterocycle. The last-mentioned approach attracts special attention because it discloses the synthetic potential and the advantages and disadvantages of heterocyclisation components and represents more vividly the methods suitable for solving sophisticated synthetic problems.

Amidines are important starting compounds in the synthesis of heterocyclic systems of various types. There are several ways of construction of heterocycles with participation of amidines

(*a*) cyclisation upon the reaction with the NH group of the amidine;

(*b*) transformation of the reactive CH groups attached to the amidine carbon atoms;

(*c*) pericyclic reactions;

(*d*) reaction of the electrophilic amidine carbon atoms with external or internal nucleophiles.

Only routes (*a*) and (*b*) have been considered comprehensively in the literature.[1–5] In this review, we analyse the prospects for using N^1,N^1-disubstituted N^2-aryl- and N^2-hetarylformamidines (hereinafter, referred to as aryl- and hetarylformamidines, respectively) for the construction of simple and fused heterocycles. These compounds cannot react by routes (*a*) and (*b*); therefore, it becomes possible to focus attention on the key reactions of types (*c*) and (*d*) and to extend the existing generalisations and views on the role of amidines in the synthesis of heterocyclic systems.

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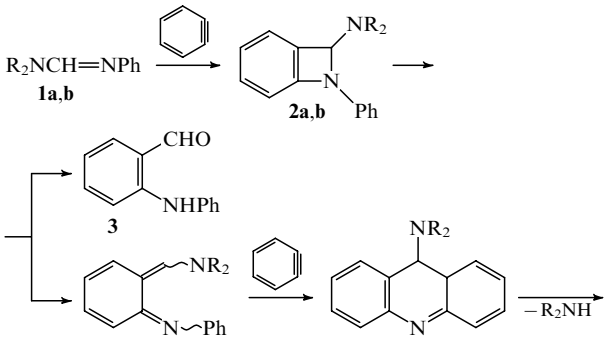
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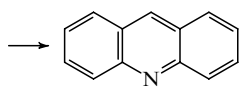
II. Pericyclic and cyclisation reactions initiated by nucleophilic addition to multiple bonds

1. Cycloaddition

N^1,N^1-Dimethyl-N^2-arylformamidines and N^1,N^1-dimethyl-N^2-hetarylformamidines can play a dual role in cycloaddition: they either provide the imine fragment of the dimethylaminomethylideneamino group $N=CHNMe_2$ (hereinafter, the amidine fragment) for heterocyclisation or act as heterodienes in which the amidine fragment N = CH is conjugated with the double bond of the substituent at the imine nitrogen atom. The latter pathway is realised only for *N*-hetarylamidines characterised by a high degree of alternation of single and double bonds. In these compounds, the double bond in a heterocyclic substituent is activated by the electron-donating amidine group;[6] hence, the Michael addition to this bond is possible. The primary reaction products can cyclise to give compounds with the same structure as those formed upon concerted [2 + 4]-cycloaddition. In these products, recyclisation of heterocyclic fragments is possible, resulting in new heterocyclic compounds.

N^1,N^1-Dimethyl-N^2-phenylformamidine **1a** and phenyliminopyrrolidinomethane **1b** react with dehydrobenzene according to the [2 + 2]-cycloaddition pattern[7] giving rise to unstable benzazetines **2a**,**b**, which are converted into 2-phenylaminobenzaldehyde **3** and acridine **4** under the reaction conditions.

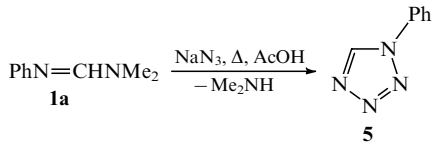




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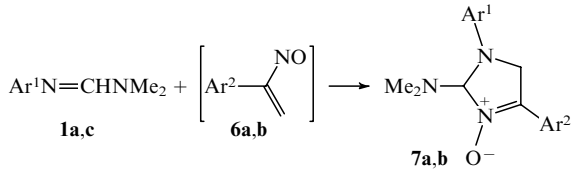
NR_2 = NMe_2 (**a**),  (**b**).

The amidine **1a** reacts with sodium azide according to the [2 + 3]-cycloaddition route to give [8] 1-phenyltetrazole **5**.



1a **5**

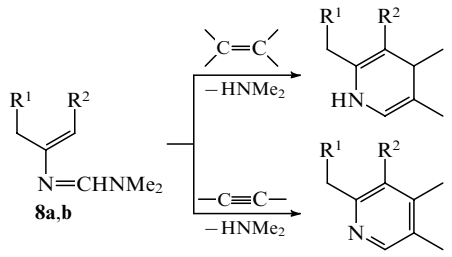
1-Nitrosovinylaryls **6a**,**b**, generated *in situ* from halooximes, react with N^1,N^1-dimethyl-N^2-arylformamidines **1a**,**c** according to the [3 + 2]-cycloaddition route to give 1,4-diaryl-2-dimethylamino-3-oxy-2,5-dihydro-1*H*-imidazoles **7a**,**b**.[9, 10]



1a,**c** **6a**,**b** **7a**,**b**

Ar^1 = Ar^2 = Ph (**1a**, **6a**, **7a**), 4-MeC_6H_4 (**1c**, **6b**, **7b**).

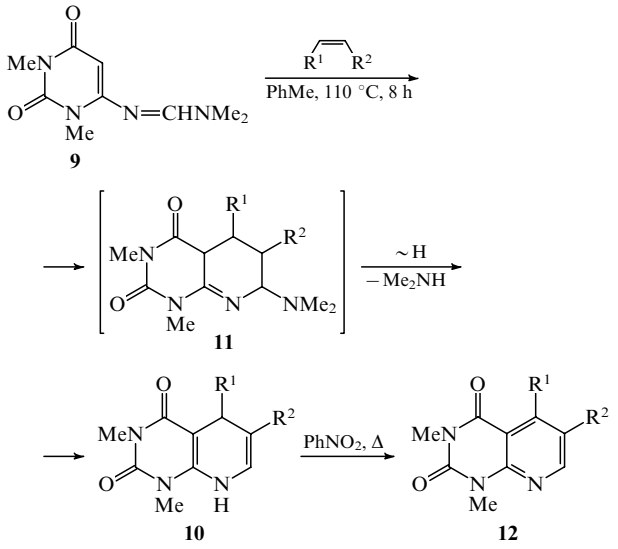
In the case of N^1,N^1-dimethyl-N^2-hetarylformamidines containing many alternating single and double bonds, heterocyclisation involves the azomethine fragment of the amidine substituent and the neighbouring vinylene fragment of the heterocycle. The diene reactivity increases in the sequence N^1,N^1-dimethyl-N^2-arylformamidines, N^1,N^1-dimethyl-N^2-hetarylformamidines and N^1,N^1-dimethyl-N^2-vinylformamidines. This is determined by the degree of participation of the vinylene fragment in conjugation. Indeed, N^1,N^1-dimethyl-N^2-phenylformamidine derivatives do not participate in cycloaddition reactions as dienes, whereas N^1,N^1-dimethyl-N^2-vinylformamidines are quite reactive dienes. On passing from *N*-vinylformamidines to *N*-hetarylformamidines, the diene reactivity decreases. N^1,N^1-Dimethyl-N^2-(isopropenyl)formamidine **8a** and N^1,N^1-dimethyl-N^2-(cyclohex-1-enyl)formamidine **8b** readily react with alkenes and alkynes [11] to give 1,4-dihydropyridine and pyridine derivatives formed as [4 + 2]-cycloaddition products.



8a,**b**

R^1 = R^2 = H (**a**); $R^1 - R^2$ = $(CH_2)_3$ (**b**).

The reactions of N^1,N^1-dimethyl-N^2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)formamidine **9** with methyl vinyl ketone, methyl acrylate, acrylonitrile and dimethyl or diethyl maleate proceed in a similar way to give 1,3-dimethyl-5,8-dihydropyrido[2,3-*d*]pyrimidine-2,4-diones **10**, which are formed from the products of primary [2 + 4]-cycloaddition **11**.[12] The high regioselectivity observed in the reactions with monosubstituted alkenes is in line with the electron-donating influence of the amidine substituent, which increases the electron density at the 5-position of amidinodimethyluracil **9**. The compounds **10** were oxidised to the corresponding 1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-diones **12** by refluxing in nitrobenzene.

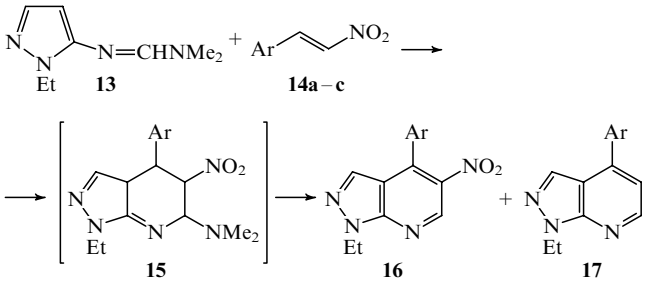


9 **11** **10** **12**

R^1 = H: R^2 = COMe, CO_2Me, CN; R^1 = R^2 = CO_2Et, CO_2Me.

N^1,N^1-Dimethyl-N^2-5-(1-ethylpyrazolyl)formamidine **13** undergoes [2 + 4]-cycloaddition to (2-nitrovinyl)benzene **14a**, 1-phenyl-3-(2-nitrovinyl)indole **14b** or 2-(2-nitrovinyl)thiophene **14c** on exposure to microwave radiation.[13] The adducts **15** formed regioselectively are converted *in situ* into a mixture of 4-aryl-1-ethyl-5-nitropyrazolo[3,4-*b*]pyridines **16** and 4-aryl-1-ethylpyrazolo[3,4-*b*]pyridines **17** as a result of abstraction of HNO_2 with aromatisation.

The ratio of the compounds **16** and **17** depends on the nature of the nitroalkene **14** but the nitro derivative **16** predominates in all cases.



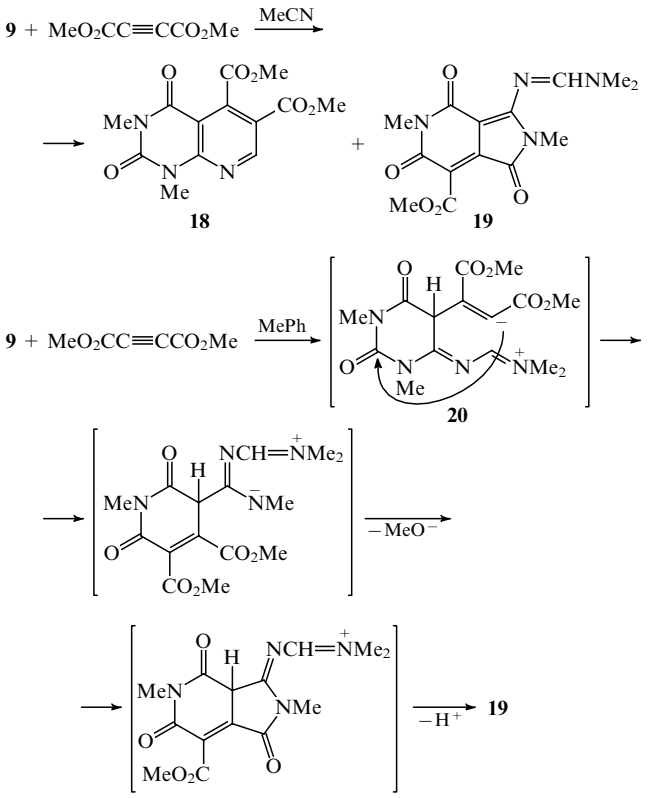
13 **14a–c** **15** **16** **17**

Nitroalkene **14**	Ar	Yield (%) **16**	**17**
a	Ph	64	8
b		60	9
c		84	–

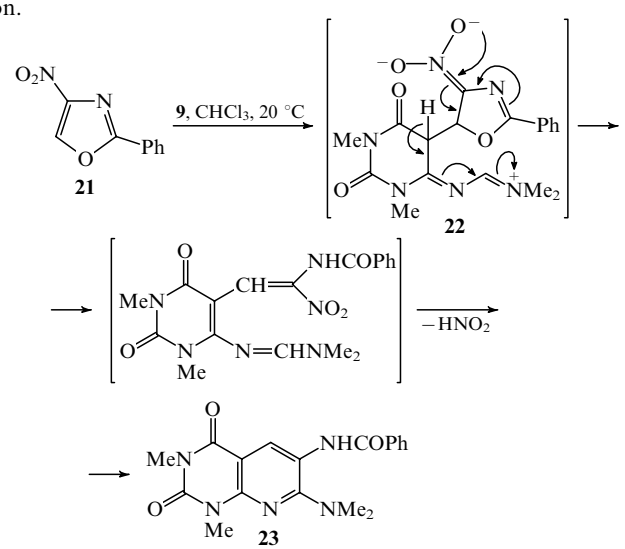
2. Recyclisation

In the reactions of heterocyclic derivatives of amidines with activated alkynes, Michael addition is the preferred reaction route, as opposed to the reactions of *N*-vinylformamidines. Indeed, the reaction of the compound **9** with dimethyl acetylenedicarboxylate in acetonitrile (20 °C, 36 h) affords a mixture of dimethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]-pyrimidine-5,6-dicarboxylate **18** and methyl 2,5-dimethyl-3-(3-methyl-1,3-diazabut-1-enyl)-1,4,6-trioxo-2,4,5,6-tetrahydropyrrolo-[3,4-*c*]pyridine-7-carboxylate **19** in 1 : 2 ratio. The reaction carried out in toluene (16 h) or chloroform (18 h) gives only the compound **19** in

70% yield. It was suggested [14] that this compound results from recyclisation of the uracil residue in the Michael addition product **20** formed initially.

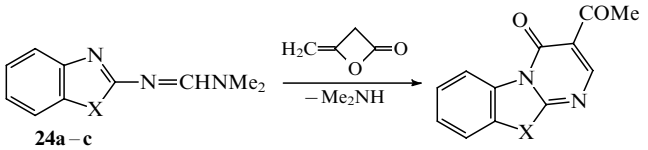


A reactive dienophile, 4-nitro-2-phenyloxazole **21**, reacts with amidinouracil **9** according to the Michael addition pathway, although its reactions with other dienes follow the [2 + 4]-cycloaddition route.[15] The intermediate **22** is converted into 6-benzamido-7-dimethylamino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine **23** through opening of the oxazole ring followed by an electrocyclic reaction accompanied by aromatisation.



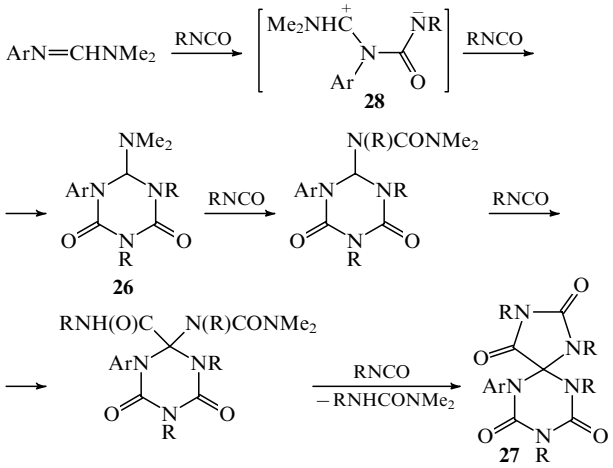
3. Reactions with diketene and isocyanates

The reactions of *N*-hetarylformamidines with diketene have been studied in relation to systems containing a pyridine nitrogen atom at the α-position relative to the amidine substituent, namely, N^1,N^1-dimethyl-N^2-benzothiazol-2-ylformamidine **24a**, N^1,N^1-dimethyl-N^2-benzoxazol-2-ylformamidine **24b** and N^1,N^1-dimethyl-N^2-benzimidazol-2-ylformamidine **24c**. These reactions proved convenient for the construction of fused pyrimidine-containing heterocycles **25a** – **c**.[16, 17]

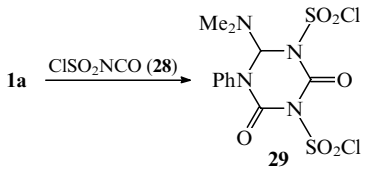


X = S (**a**), O (**b**), NH (**c**).

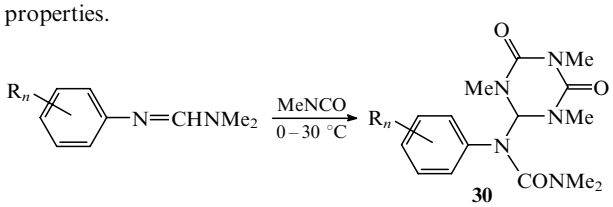
In the general case, N^1,N^1-dimethyl-N^2-arylformamidines react with aryl isocyanates to give 1 : 2 adducts, 1,3,5-triazines **26**.[18, 19] However, apart from these products, the reactions afford solid substances with high melting points, which have been identified [20 – 22] as 1,3,6,8,10-pentaazaspiro[4.5]decane-2,4,7,9-tetraones **27**. Presumably,[20, 22] they are formed *via* bipolar intermediate **28**, which regioselectively adds isocyanate giving rise to *sym*-triazinedione **26**. Successive insertion of isocyanate into the C – N and C – H bonds results in the spiro compound **27**.



4-Dimethylamino-2,6-dioxo-5-phenyl-4,5-dihydro-1,3,5-triazine-1,3-disulfonyl dichloride **29** is produced in the reaction of the amidine **1a** with Graf's isocyanate **28**.[23]



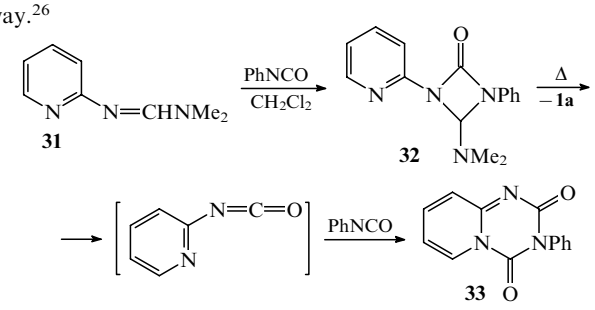
An unusual cycloaddition of methyl isocyanate to N^1,N^1-dimethyl-N^2-arylformamidines has been proposed [24] as a method for the synthesis of 3-aryl-1,1-dimethyl-3-(1,3,5-trimethyl-4,6-dioxo-1,2-dihydro-1,3,5-triazin-2-yl)ureas **30**, possessing herbicidal properties.



R_n = H, Cl, Cl_2, 3-CF_3, 4-MeO, 4-Me, 3-Cl-4-MeO, 3-Cl-4-Me, 3-CF_3-4-Cl.

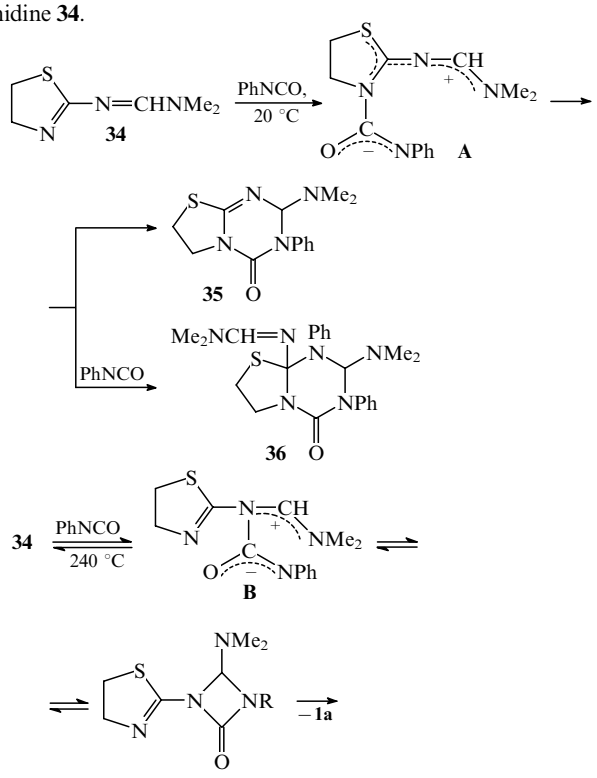
Some reactions of *N*-hetarylformamidines with isocyanates differ from the transformations of *N*-arylamidines because either heteroatoms or activated multiple bonds of the heterocycle are involved in the reaction. Thus the reaction of N^1,N^1-dimethyl-N^2-2-pyridylformamidines **31** with phenyl isocyanate gave a [2 + 2]-cycloadduct, 4-dimethylamino-1-phenyl-3-pyridin-2-yl-1,3-diazetidin-2-one **32**, in a high yield. At elevated temperature in the presence of phenyl isocyanate, this product is converted into

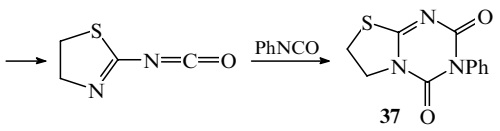
3-phenylpyrido[1,2-*a*]-1,3,5-triazine-2,4-dione **33**.[25] 3-Phenylpyridazino[1,6-*a*]-1,3,5-triazine-2,4-dione is prepared in a similar way.[26]



Presumably,[25] the cycloadduct **32** formed initially undergoes cyclodegradation at elevated temperatures. The subsequent [2 + 4]-cycloaddition of the resulting isocyanates gives rise to the bicyclic adduct **33**.

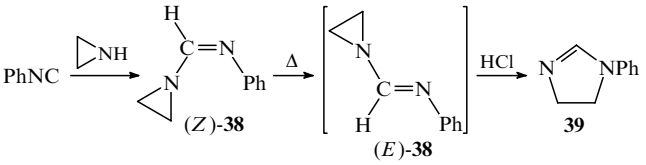
Depending on the temperature and the reactant ratio, the reactions of N^1,N^1-dimethyl-N^2-2-(4,5-dihydrothiazol-2-yl)formamidines **34** with phenyl isocyanate afford different products, 2-dimethylamino-3-phenyl-2,3,6,7-tetrahydrothiazolo[3,2-*a*]-1,3,5-triazin-4-one **35**, N^1,*N*-dimethyl-N^2-(2-dimethylamino-4-oxo-1,3-diphenylhexahydrothiazolo[3,2-*a*]-1,3,5-triazin-8*a*-yl)formamidine **36** or 3-phenyl-6,7-dihydrothiazolo[3,2-*a*]-1,3,5-triazine-2,4-dione **37**.[27] In the opinion of the researchers cited, phenyl isocyanate reacts with the endocyclic imine nitrogen atom of the hetarylamidine **34** at room temperature; this gives rise to intermediate bipolar compound **A**. This compound either cyclises to yield compound **35** or reacts with a second phenyl isocyanate molecule, resulting in the amidine **36**. At elevated temperatures, the attack by phenyl isocyanate on the exocyclic imine nitrogen atom of the amidine **34** proves to be the preferred reaction pathway; this gives initially intermediate **B**, which is converted into compound **37** upon the reaction with phenyl isocyanate. Apparently, an important stage of this transformation in the latter case is transamination, *i.e.* the exchange by the imine fragments between phenyl isocyanate and the amidine **34**.





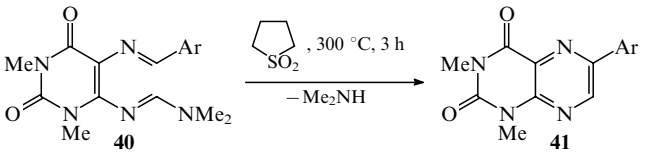
4. Electrocyclic reactions

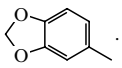
The transformation of phenyliminoaziridinomethane **38** into 1-phenyl-4,5-dihydro-1*H*-imidazoline **39** induced by nucleophiles or acids proceeds similarly to the symmetry-allowed synchronous isomerisation of vinylcyclopropane into cyclopentene. The rearrangement is similar to the isomerization of vinylethyleneimine into pyrroline. The researchers suggested [28, 29] that the reaction of aziridine with phenyl isocyanide gives rise to thermodynamically unstable *Z*-isomer **38**, the transformation of which into the imidazoline **39** proceeds *via* initial *Z*,*E*-isomerization.



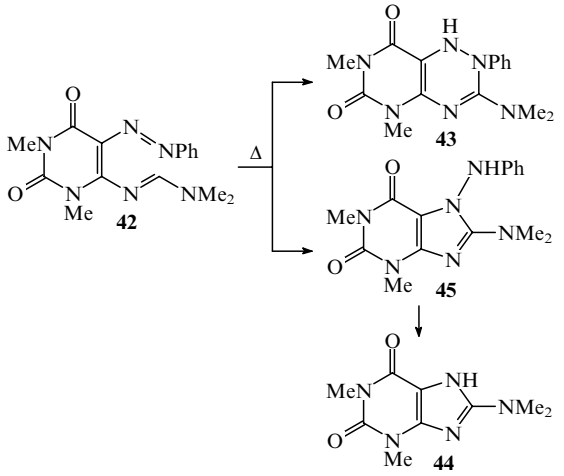
On heating or irradiation, *N*-hetarylamidines containing a substituent with an unsaturated fragment in the neighbouring position to the amidine group undergo sigmatropic transformations giving rise to more complicated heterocyclic systems.

Thermolysis of N^1,N^1-dimethyl-N^2-6-(5-arylideneamino-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)formamidine **40** is accompanied by the aza Cope reaction. An intramolecular pericyclic reaction followed by isomerisation and elimination of dimethylamine affords 6-substituted 1,3-dimethylpteridine-2,4-dione **41**.[30]

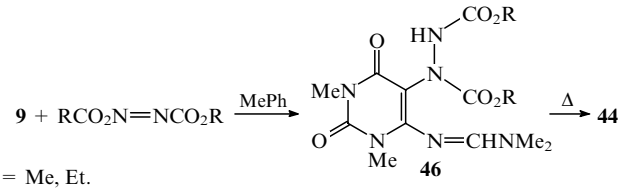


Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, .

Transformations of this type are also typical of systems containing an azo fragment in the neighbouring position to the amidine substituent, although they are accompanied by side processes. Thus N^1,N^1-dimethyl-N^2-6-(1,3-dimethyl-2,6-dioxo-5-phenylazo-1,2,3,6-tetrahydropyrimidin-4-yl)formamidine **42** is converted at 210–220 °C into a mixture of 3-dimethylamino-5,7-dimethyl-2-phenyl-1,5-dihydro-2*H*-pyrimido[4,5-*e*]-1,2,4-triazine-6,8-dione **43** and 8-dimethylamino-1,3-dimethylpyrine-2,6-dione **44**. Apparently, the latter product is formed from 9-anilino-8-dimethylamino-1,3-dimethylpurine-2,6-dione **45**.[31]

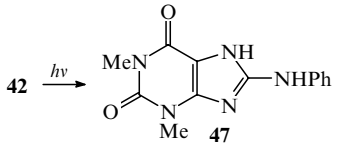


The reactions of amidinouracil **9** with azodicarboxylates proceed similarly to transformations of 6-amino- or 6-alkylaminouracils to give adducts **46**. These products are converted into pyrine derivatives **44** upon thermal cyclisation.[14]

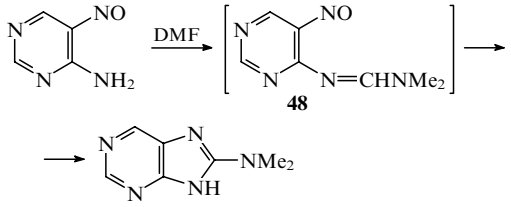


R = Me, Et.

In the photolysis of formamidine **42**, 1,5-cycloaddition is the predominant reaction pathway;[32,33] 8-phenylamino-1,3-dimethylpurine-2,6-dione **47** is formed upon irradiation. A similar transformation takes place in the reductive heterocyclisation of the compound **42** induced by sodium dithionite.[34]



The intramolecular 1,5-cycloaddition in N^1,N^1-dimethyl-N^2-(5-nitrosopyrimidin-4-yl)formamidine **48** proceeds at room temperature without irradiation.[35]



III. Intramolecular nucleophilic substitution

1. Reactions with participation of N-nucleophiles

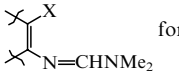
N^1,N^1-Dimethyl-N^2-arylformamidines and N^1,N^1-dimethyl-N^2-hetarylformamidines are convenient objects for heterocyclisation, provided that a position adjacent to the amidine substituent is occupied by a reactive functional group (amino, carbonyl, ethoxycarbonyl, nitrile, iminophosphorane group and so on).

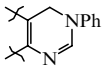
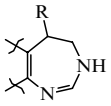
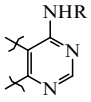
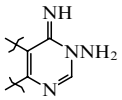
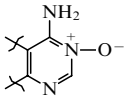
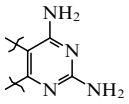
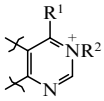
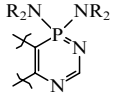
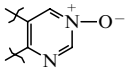
The reactions in which an N-nucleophile reacts with formamidine in the key stage of ring formation are summarised in Table 1. It should be emphasised that this approach is especially attractive for the synthesis of fused systems which include five-, six- and seven-membered nitrogen-containing heterocyclic fragments. The use of functionalised amidines in the synthesis of various fused pyrimidines has been studied most thoroughly.

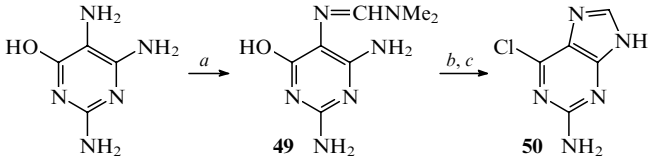
Cyclisation can either involve a nitrogen-containing nucleophile present in the molecule or occur upon the addition of ammonia, amines, hydroxylamine, their salts and hydrazine or guanidine. In some cases, the reaction is accompanied by deamidination, *i.e.* transformation of the amidine substituent into an amino group.

Aryl- and hetarylformamidines containing a free amino group in the position neighbouring to the amidine substituent are postulated as intermediates in several syntheses of imidazoles from 1,2-diamines. Meanwhile, N^2-(2,4-diamino-6-hydroxypyrimidin-5-yl)-N^1,N^1-dimethylformamidine **49** is a stable compound because the electron-donating substituents in the pyrimidine ring decrease the electrophilicity of the formamidine carbon atom.

Formamidines **49** can be converted into 2-amino-6-chloropurine **50** on treatment with HCl and subsequent heating.[36]

Table 1. Products of heterocyclisation of aryl- and hetarylformamidines  formed with participation of N-nucleophiles.

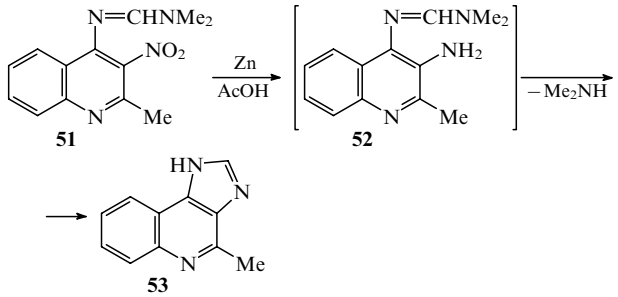
Type of reaction	X	Reagent or reaction conditions	Reaction product
a	NH_2	Δ	
b	CH_2NHPh	Δ	
c	$CH(R)CH_2NH_2$	Δ	
d	CN	RNH_2	
e	CN	H_2NNH_2	
f	CN	H_2NOH	
g	CN	$(H_2N)_2C=NH$	
h	C(O)R	NH_3	
i	$C(O)R^1$	R^2NH_2	
j	CO_2Et	RNH_2	
k	$P^+(Cl)(NR_2)_2Cl^-$	NH_3	
l	CHO	NH_2OH	



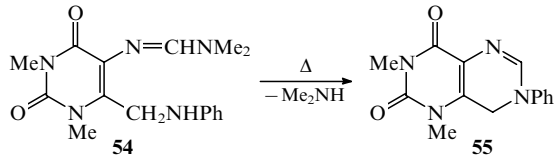
(*a*) $POCl_3$, DMF; (*b*) HCl, H_2O; (*c*) Δ, $-Me_2NH\cdot HCl$.

Hetarylamidines containing a free amino group are synthesised by selective reduction of nitro- or cyano-substituted amidines. Under the reaction conditions, they undergo heterocyclisation according to route *a* (see Introduction) giving rise to an imidazole fragment. Thus reduction of N^1,N^1-dimethyl-N^2-(2-methyl-3-nitroquinolin-4-yl)formamidine **51** results in N^2-(3-amino-2-

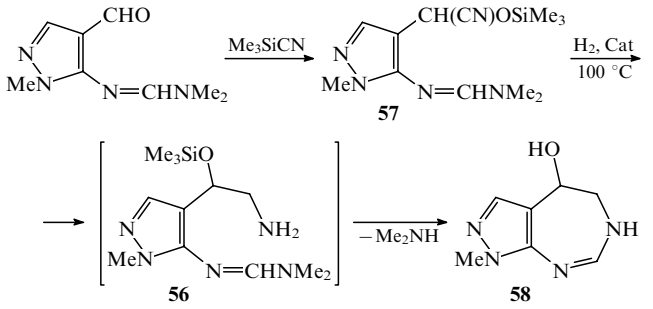
methylquinolin-4-yl)-N^1,N^1-dimethylformamidine **52**, which undergoes intramolecular cyclisation *in situ* to give 4-methylimidazo[4,5-*c*]quinoline **53**.[37]



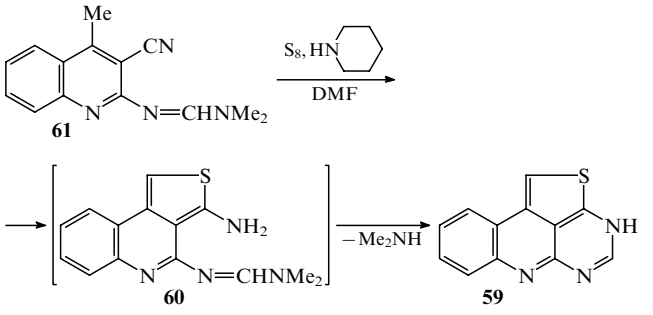
The electron-donating effect of the dimethyluracil moiety accounts for the stability of N^1,N^1-dimethyl-N^2-(1,3-dimethyl-2,4-dioxo-6-phenylaminomethyl-1,2,3,4-tetrahydropyrimidin-5-yl)formamidine **54**; it is converted into 1,3-dimethyl-7-phenyl-7,8-dihydropyrimido[5,4-*d*]pyrimidine-2,4-dione **55** only on heating in toluene.[38]



Cyclisation *in situ* of N^1,N^1-dimethyl-N^2-[4-(2-amino-1-trimethylsilyloxyethyl)-1-methylpyrazol-5-yl]formamidine **56**, prepared by the reduction of N^1,N^1-dimethyl-N^2-[4-(cyano-trimethylsilyloxymethyl)-1-methylpyrazol-5-yl]formamidine **57**, is a key stage in the synthesis of 1-methyl-1,4,5,6-tetrahydropyrazolo[3,4-*d*]-1,3-diazepin-4-ol **58**.[39–41]

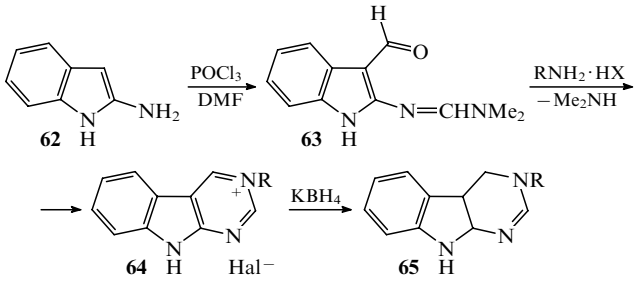


In the synthesis of 3*H*-2-thia-3,5,6-triazaaceanthrylene **59**, the key intermediate, formamidine **60**, containing a free amino group, is prepared using the Gewald heterocyclisation of N^1,N^1-dimethyl-N^2-(4-methyl-3-cyanoquinolin-2-yl)formamidine **61**.[42]



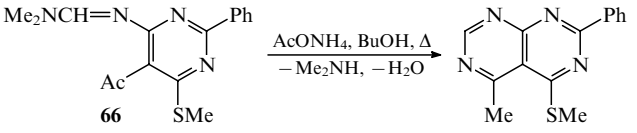
The reactions of compounds containing cyano-, ester or cabonyl group in the position adjacent to the amidine substituent with ammonia derivatives (see Table 1, reactions *d*–*j*) are widely used to form a fused pyrimidine fragment. In some cases, the reaction with ammonia is accompanied by deamidination.

On treatment with excess Vilsmeier reagent, reactive amino-substituted heterocyclic compounds are converted into formylhetarylformamidines.[43] For example, 2-aminoindole **62** was used to synthesise N^1,N^1-dimethyl-N^2-(3-formylindol-2-yl)formamidine **63**.[44] Refluxing this product with ammonium salts in ethanol induces cyclisation giving rise to salt **64** the subsequent reduction of which affords 3-substituted 2,3,4,4*a*-tetrahydropyrimido[4,5-*b*]indole **65**. This type of cyclisation has been studied in relation to hetarylamidines derived from 3-aminoindole[45,46] or 3- and 5-aminopyrazoles.[47,48]

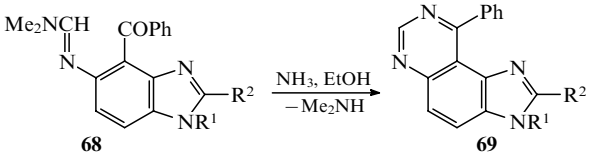


X = Cl, Br; R = CH_2COOH, Et, Ph, $(CH_2)_2NMe_2$, $(CH_2)_3OH$.

The behaviour of hetarylformamidines having an acetyl group in the position adjacent to the amidine substituent with respect to low-basicity nitrogen-containing nucleophiles is similar to the behaviour of formyl-substituted derivatives.[49,50] Thus N^1,N^1-dimethyl-N^2-(5-acetyl-6-methylthio-2-phenylpyrimidin-4-yl)formamidine **66** is converted into 5-methyl-4-methylthio-2-phenylpyrimido[4,5-*d*]pyrimidine **67** when heated with ammonium acetate in butyl alcohol.[51]

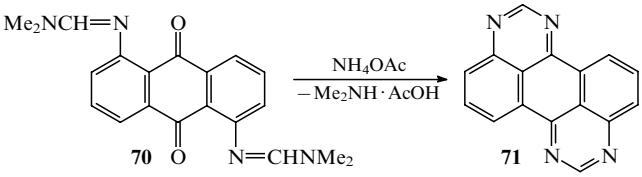


1,2-Disubstituted N^1,N^1-dimethyl-N^2-(4-benzoyl-1*H*-benzimidazol-5-yl)formamidine **68**, containing a low-reactivity carbonyl group, is transformed into substituted 9-phenyl-3*H*-imidazo[4,5-*f*]quinazoline **69** only upon prolonged heating in an ethanol solution of ammonia in an autoclave.[52]



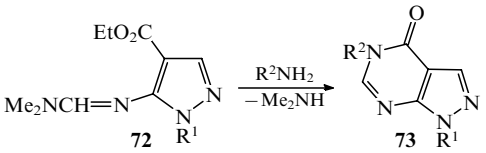
R^1 = CH_2CH_2OH, Ph; R^2 = H, Me.

The carbonyl groups of anthraquinone can also be involved in the amidine cyclisations.[53,54] For example, 1,5-bis(3-methyl-1,3-diazabut-1-enyl)-9,10-dioxo-9,10-dihydroanthracene **70** is converted into 1,3,7,9-tetraazaperylene **71** on refluxing with ammonium acetate in ethylene glycol methyl ether.[55] This reaction proved convenient for the synthesis of anthrapyrimidine dyes.[56,57]



The reactions of alkylamines with hetarylamidines containing an ethoxycarbonyl group next to the amidine substituent provide the possibility of constructing a pyrimidone fragment. Thus ethyl 5-(3-methyl-1,3-diazabut-1-enyl)-1*H*-pyrazolyl-4-carboxylates **72** were used to synthesise 5-substituted pyrazolo[3,4-*d*]pyrimidin-4-

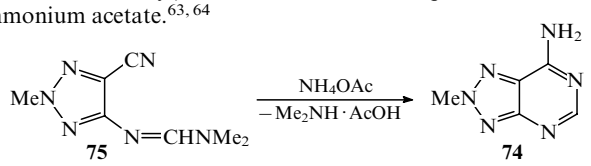
ones **73**.[58] 3-Benzyl-7-methylpyrido[2,3-*d*]pyrimidin-4-one was prepared in a similar way from the corresponding pyridine derivative.[59]



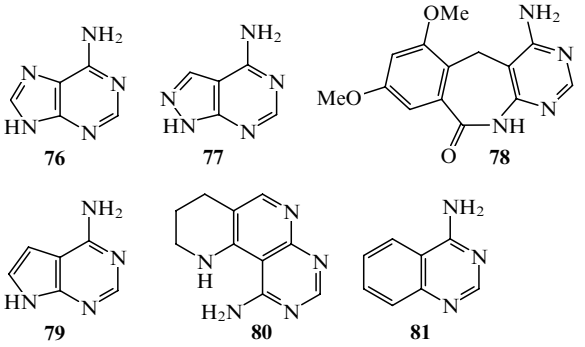
R^1 = H, Ph; R^2 = CH_2Ph, CH_2CH_2Ph, $MeCHCH_2Ph$.

The reactions of nitriles with nitrogen-containing nucleophiles are widely used to synthesise heterocyclic compounds.[60,61] Thus the reactions of aryl- and hetaryl-formamidines containing a cyano group in the position adjacent to the amidine substituent with ammonia, amines or their salts were found to be convenient for the preparation of fused aminopyrimidines. This approach is used in combinatorial chemistry.[62]

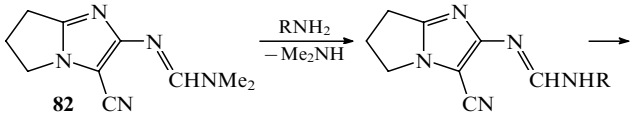
7-Amino-2-methyl-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine **74** was obtained by refluxing N^1,N^1-dimethyl-N^2-(5-cyano-2-methyl-2*H*-1,2,3-triazol-4-yl)formamidine **75** in an aqueous solution of ammonium acetate.[63,64]

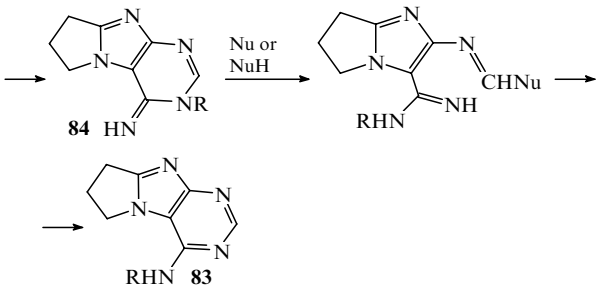


The same strategy was employed to prepare adenine **76**,[65] 4-aminopyrazolo[3,4-*d*]pyrimidine **77**,[66–69] 4-amino-6,8-dimethoxy-5-hydrobenzo[*e*]pyrimido[4,5-*b*]azepin-10-one **78**,[70] 4-aminopyrrolo[2,3-*d*]pyrimidine **79**,[71] 5,6,7,8-tetrahydro-1,3,5,10-tetraazaphenanthren-4-ylamine **80**,[72] 4-aminoquinazoline **81**[73] and their derivatives.



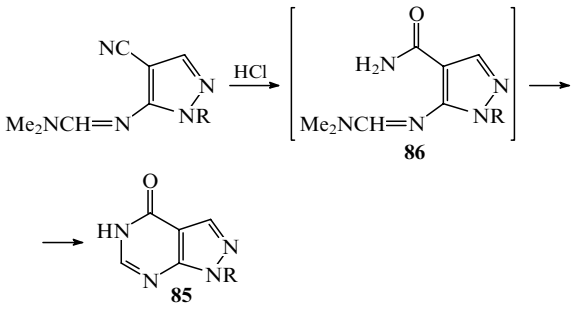
The transformation of N^1,N^1-dimethyl-N^2-(3-cyano-5,6,7-trihydropyrrolo[1,2-*a*]imidazol-2-yl)formamidine **82** into substituted 4-amino-5,6,7-trihydropyrrolo[2,1-*f*]purines **83** has been studied and a mechanism has been proposed for this reaction.[74] Presumably, the reaction starts with transamination at the formamidine carbon atom, accompanied by evolution of dimethylamine. This is followed by an intramolecular attack by the NH group on the cyano carbon atom giving rise to 5-substituted 4-imino-5,6,7-trihydropyrrolo[2,1-*f*]purines **84**. On treatment with nucleophiles, the products **84** undergo the Dimroth rearrangement; as a result, the aminopyrimidine fragment adds to the initial heterocyclic system.



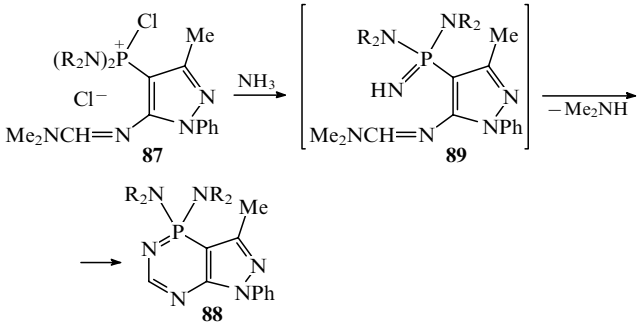


Nu = OH^-, EtO^-; NuH = HOH, EtOH, RNH_2.

Partial hydrolysis of hetarylformamidines containing a cyano group in the position adjacent to the amidine group is accompanied by heterocyclisation which gives a pyrimidone fragment. Thus treatment of 5-dimethylaminomethylideneamino-4-cyanopyrazoles substituted at the 1-position yields pyrazolo[3,4-*d*]pyrimidin-4-ones **85**. Apparently, the cyclisation proceeds *via* amides **86**.[75]

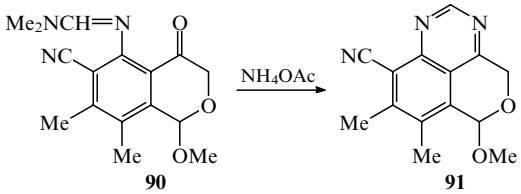


Cyclisation of hetarylformamidines can be used to prepare organophosphorus compounds.[76,77] For example, the phosphorus salts **87** cyclise on treatment with ammonia to yield 3-methyl-4,4-bis(amino)-1-phenylpyrazolo[4,5-*e*]-1,3,4λ^5-diazaphosphinines **88** *via* intermediate iminophosphonic diamides **89**.[78]

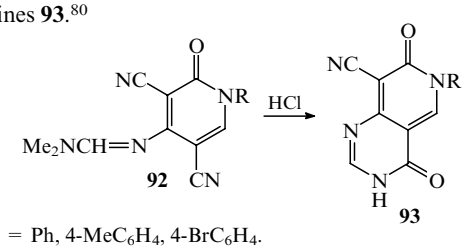


NR$_2$ = , NEt_2.

When the amidine molecule incorporates two different reaction sites which occupy positions neighbouring the amidine group, the more reactive site participates predominantly in the cyclisation. For instance, N^1,N^1-dimethyl-N^2-(1-methoxy-7,8-dimethyl-4-oxo-6-cyanoisochroman-5-yl)formamidine **90** is converted into 6-methoxy-7,8-dimethyl-4*H*,6*H*-5-oxa-1,3-diazaphenalene-9-carbonitrile **91**, the cyano group remaining intact during the reaction.[79]

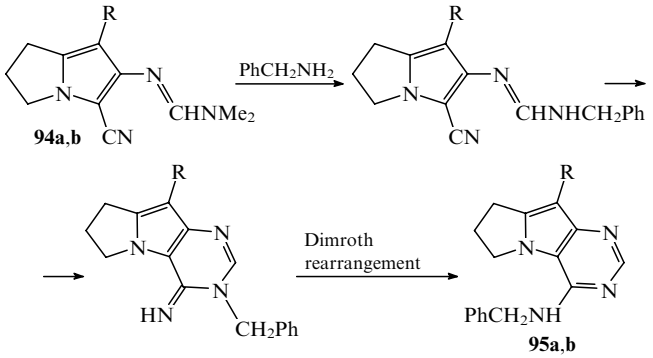


The same functional groups located in different positions of the heterocycle can differ substantially in reactivity. Thus heterocyclisation of dicyano-substituted 4-dimethylaminomethylideneamino-2-oxo-1,2-dihydropyridines **92** occurs selectively giving rise to 8-cyano-4,7-dioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidines **93**.[80]



R = Ph, 4-MeC_6H_4, 4-BrC_6H_4.

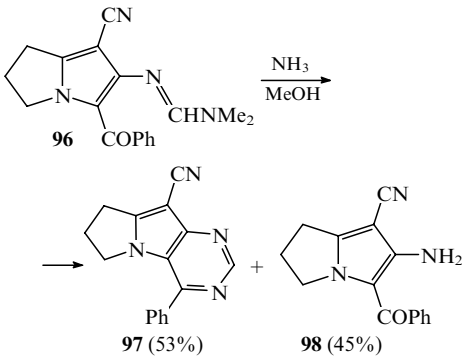
The reaction of N^1,N^1-dimethyl-N^2-(5,7-dicyano-2,3-dihydro-1*H*-pyrrolizin-6-yl)formamidine **94a** with benzylamine involves the 5-cyano group and results in 8-benzylamino-4-cyano-2,3-dihydro-1*H*-pyrrolo[1′,2′:5,1]pyrrolo[2,3-*d*]pyrimidine **95a**. The second cyano group does not participate in the reaction. In the case where different functional groups are present in the positions neighbouring the amidine substituent, the cyclisation pathway depends not only on the reactivity of each group but also on their positions in the ring. Indeed, in the cyclisation of N^1,N^1-dimethyl-N^2-(5-cyano-7-ethoxycarbonyl-2,3-dihydro-1*H*-pyrrolizin-6-yl)-formamidine **94b**, the more reactive cyano group is involved in the reaction, which affords 8-benzylamino-4-ethoxycarbonyl-2,3-dihydro-1*H*-pyrrolo[1′,2′:5,1]pyrrolo[2,3-*d*]pyrimidine **95b**.[81]



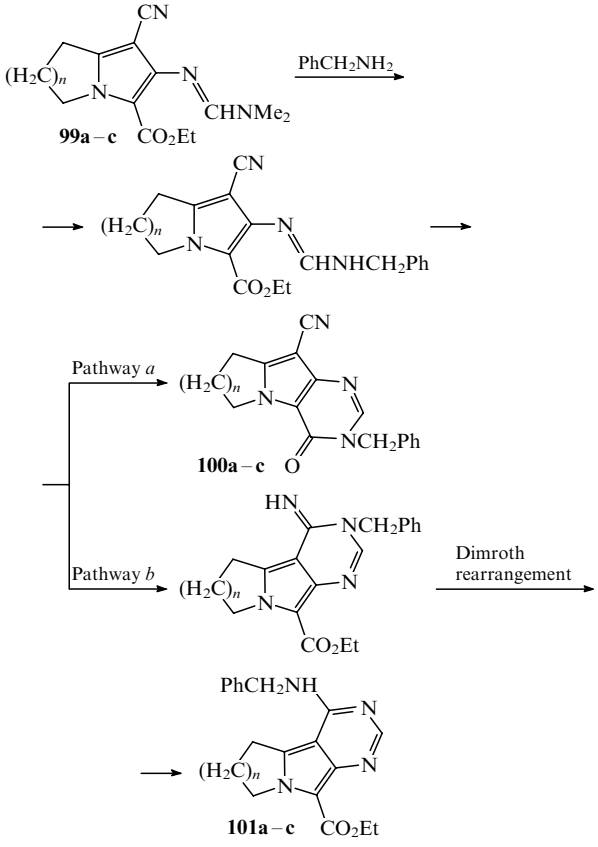
R = CN (**a**), COOEt (**b**).

The fact that the reaction follows only this pathway can appear unexpected because the α-position of the unsubstituted pyrrole ring is enriched in electron density, and the cyclisation would rather be expected to involve the electrophilic substituent located in the less electron enriched β-position. However, the presence of two electron-withdrawing groups induces redistribution of the partial charges on the carbon atoms of the ring in both the ground and transition states. As a consequence, the electronic effects of the heterocyclic fragment of the molecule substantially change. In the above example, the reactivity of the nitrile group in the α-position of the pyrrole ring increases and, hence, cyclisation is highly regioselective. The assumption concerning electron density redistribution is supported by the fact that the ester groups at the 4-position of 2,4-pyrroledicarboxylic acid diesters are more stable against hydrolysis than the 2-ester groups.[82]

In the case of 5-benzoyl-7-cyano-6-(3-methyl-1,3-diazabut-1-enyl)-2,3-dihydro-1*H*-pyrrolizine **96**, the carbonyl group is much more reactive than the nitrile group; therefore, cyclisation affords 4-cyano-8-phenyl-2,3-dihydro-1*H*-pyrrolo[1′,2′:5,1]pyrrolo[2,3-*d*]-pyrimidine **97**. The reaction is accompanied by deamidination, which gives compound **98**.[83]



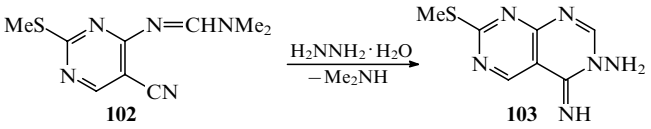
Kadushkin *et al.*[84] have studied the influence of the size of the ring fused to the pyrrole fragment on the pathway of cyclisation of polymethylenepyrrole derivatives, namely, 7-cyano-6-dimethylaminomethylideneamino-5-ethoxycarbonyl-2,3-dihydro-1*H*-pyrrolizine **99a**, 1-cyano-2-dimethylaminomethylideneamino-3-ethoxycarbonyl-5,6,7,8-tetrahydroindolizine **99b** and 1-cyano-2-dimethylaminomethylideneamino-3-ethoxycarbonyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine **99c**.



Compound	*n*	Yield (%)	
		100	**101**
a	1	< 5	79
b	2	40	42
c	3	95	< 5

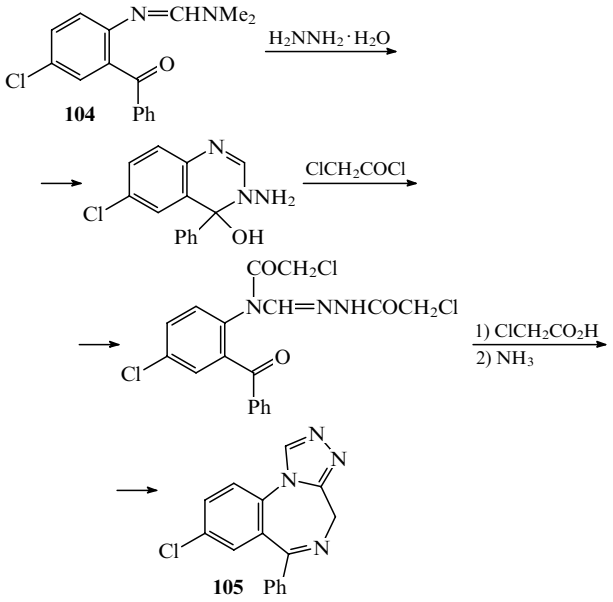
In the case of the compound **99a**, pathway *b* predominates, *i.e.* the reaction involves the nitrile group and gives compound **101a**. When the ring size and, hence, steric overcrowding, increases, the heterocyclisation involves the ethoxycarbonyl group activated by the neighbouring heterocyclic fragment. The contribution of pathway *a* increases and, correspondingly, the compounds **100b**,**c** are formed in higher yields.

Hydrazine hydrate is also used to perform cyclisation of hetarylformamidines containing a nitrile or carbonyl group in the position adjacent to the amidine substituent. Thus 5-cyano-4-dimethylaminomethylideneamino-2-methylthiopyrimidine **102** reacts with hydrazine hydrate being thus converted into 3-amino-4-imino-7-methylthio-3,4-dihydropyrimido[4,5-*d*]pyrimidine **103**.[85] However, in some cases, only deamidination is observed in these reactions instead of cyclisation.[86]



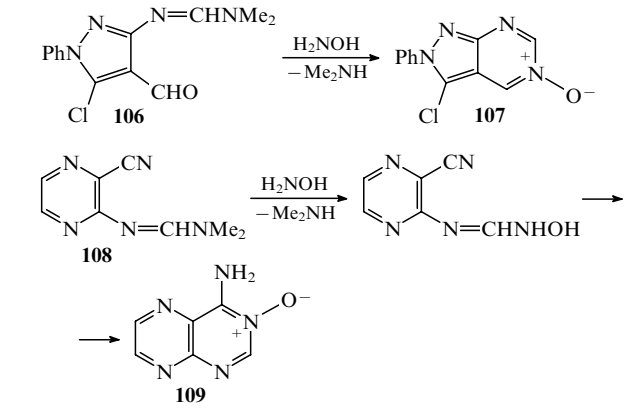
102 **103**

Since the formation of a pyrimidine ring is more favourable than the formation of a 1,2,4-triazepine ring,[87] only one nitrogen of the hydrazine molecule participates in the cyclisation.[88–90] The free amino group can be used in subsequent transformations. Thus the reaction of N^1,N^1-dimethyl-N^2-(2-benzoyl-4-chlorophenyl)formamidine **104** with hydrazine hydrate has served as the first stage in the synthesis of *symm*-triazolo[4,3-*a*]-1,4-benzodiazepine derivatives **105**.[91]



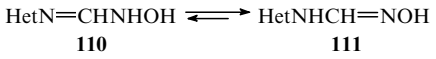
104 **105**

Treatment with hydroxylamine of hetarylformamidines containing a carbonyl or cyano group neighbouring an amidine group gives rise to pyrimidine *N*-oxides.[44–47, 92, 93] For instance, 5-chloro-3-dimethylaminomethylideneamino-4-formyl-1-phenylpyrazole **106** was converted into 3-chloro-5-oxy-2-phenylpyrazolo[3,4-*d*]pyrimidine **107**, while 3-cyano-2-dimethylaminomethylideneaminopyrazine **108** was transformed into 4-amino-3-oxypteridine **109**.



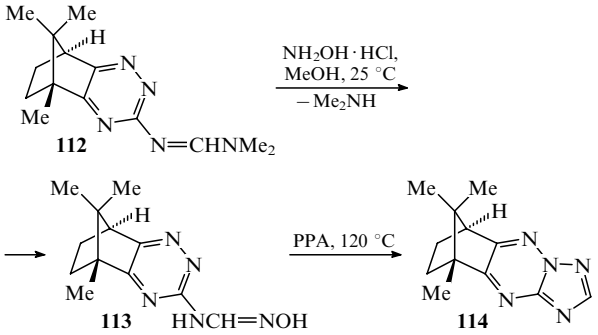
106 **107** **108** **109**

It should be emphasised that, unlike the reactions with ammonia, hydrazine or their salts, in this case, the initial product of replacement of the dialkylamino group **110** can be detected and, in some instances, isolated. This difference is due to the fact that the initial reaction product **110** is equilibrated with its tautomer **111**, the latter predominating in the reaction mixture. Compounds of the type **111** do not tend to undergo heterocyclisation, which proceeds more slowly.



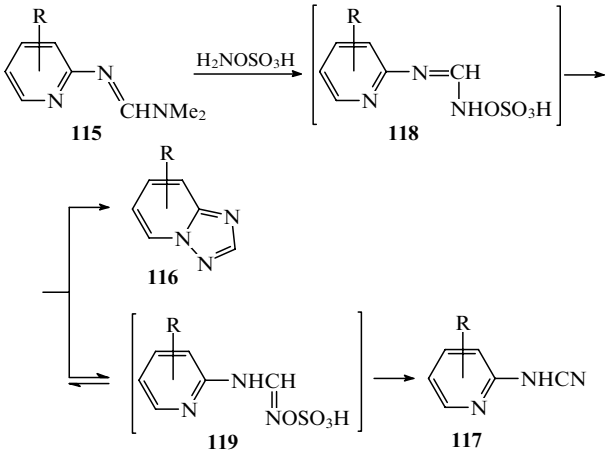
110 **111**

N-Hetarylformamidines in which the amidine substituent occupies the neighbouring position with respect to the pyridine-type nitrogen atom [94] can be used to synthesise fused heterocycles containing a 1,2,4-triazole fragment.[95] For example, 4-dimethylaminomethylideneamino-1,11,11-trimethyl-3,5,6-triazatricyclo-[6.2.1.$0^{2,7}$]undeca-2,4,6-triene **112** was converted into 11,14,14-trimethyl-3,4,5,7,9-pentacyclo[9.2.1.$0^{2,9}$.$0^{4,8}$]tetradeca-2,5,7,9-tetraene **113** in a high yield.[96] The triazole fragment (compound **114**) is formed upon nucleophilic attack by a ring nitrogen atom on the nitrogen atom attached to the hydroxy group in the product **113** formed in the reaction with hydroxylamine. The cyclisation occurs on treatment with polyphosphoric acid (PPA) with heating. The high potential of this approach was also demonstrated in relation to derivatives of pyridine,[97] pyrimidine,[98] pyridazine,[89] pyrazine,[99] *symm*-triazine and some other polycyclic systems.[73, 100, 101]



112 **113** **114**

Apparently, cyclisation induced by hydroxylaminesulfuric acid follows a similar route.[102, 103] Thus N^1,N^1-dimethyl-N^2-2-pyridylformamidine derivatives **115** are converted into the corresponding 1,2,4-triazolo[1,5-*a*]pyridines **116**. 2-Pyridylcyanoamides **117** are formed as side products. Presumably, the dimethylamino group is initially replaced by hydroxylaminesulfuric acid giving rise to compound **118**, which cyclises. The side product **117** is produced from tautomer **119**.

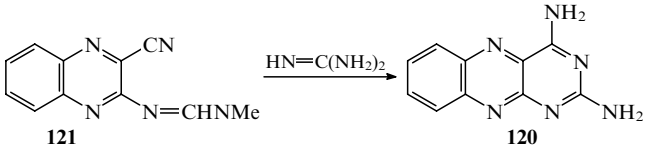


115 **118** **116** **119** **117**

R = H, 2-Me, 3-Me, 4-Me.

When hetarylamidines containing a cyano group near the amidine function are subjected to cyclisation on treatment with

guanidine, two amino groups are incorporated simultaneously into the pyrimidine ring formed. This approach was used to prepare 2,4-diaminopyrimido[4,5-*b*]quinoxaline **120** from 3-cyano-2-dimethylaminomethylideneaminoquinoxaline **121**.[104]



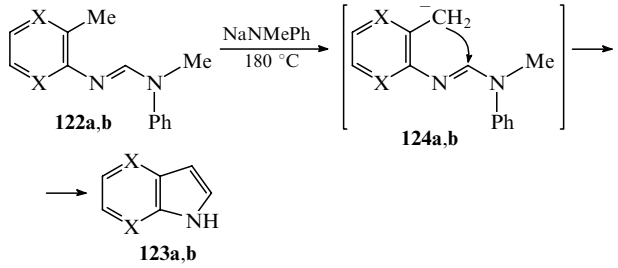
121 **120**

2. Reactions involving C-nucleophiles

Cyclisations of hetarylamidines in which the substitution of the amidine amino group gives rise to a C−C bond are presented in a general form in Table 2.

As in the case of *N*-nucleophiles, this approach permits the construction of five-, six- and seven-membered heterocycles.

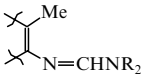
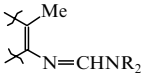
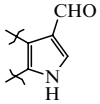
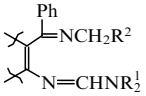
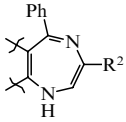
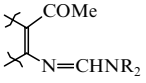
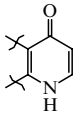
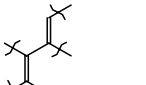
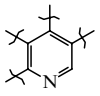
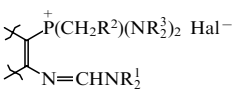
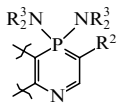
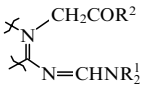
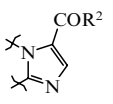
Aryl- and hetarylformamidines containing a methyl group next to an amidine group are converted into heteroannelated pyrroles on heating with sodium phenylmethylamide in methylaniline.[105, 106] Thus 2-dimethylaminomethylideneamino-3-



122a,**b** **124a**,**b** **123a**,**b**

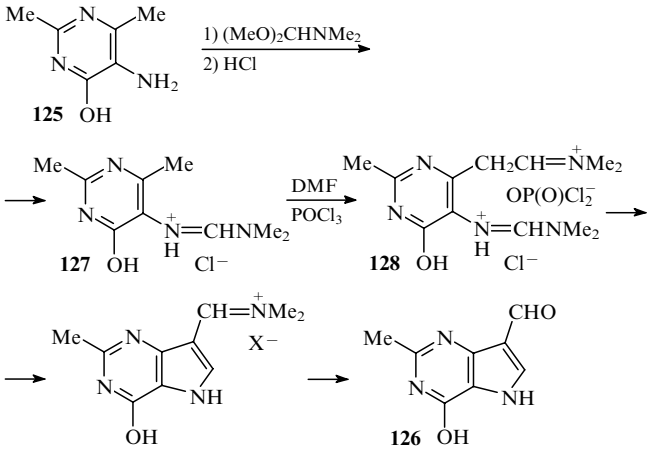
X = N (**a**), CH (**b**).

Table 2. Products of cyclisation of hetarylamidines formed on treatment with C-nucleophiles.

Type of reaction	Hetarylamidine	Reagent or reaction conditions	Reaction product
a		B: or flash pyrolysis	
b		$POCl_3$–DMF	
c		Δ	
d		B:	
e		CF_3CO_2H	
f		B:	
g		B:	

methylpyrazine **122a** is transformed into 5*H*-pyrrolo[2,3-*b*]pyrazine **123a**. The indole **123b** was prepared from N^1,N^1-dimethyl-N^2-2-tolylformamidine **122b** in a similar way. This process can be regarded as a modified Madelung synthesis of indoles.[107] The reaction occurs in the presence of strong bases *via* intermediate carbanions **124a**,**b**, or under conditions of vacuum flash pyrolysis.[108]

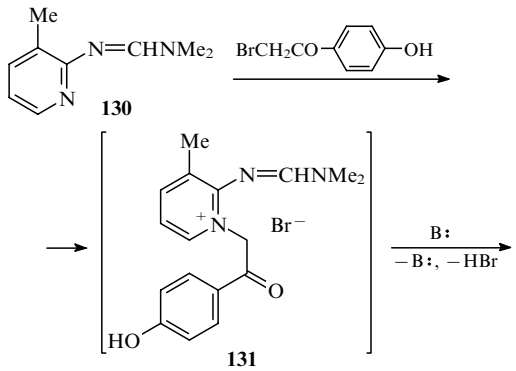
Treatment of heterocyclic compounds having methyl and amino groups in the vicinal positions with excess Vilsmeier reagent results in the formation of a pyrrole fragment containing a β-formyl group.[109, 110] For example, 5-amino-4-hydroxy-2,6-dimethylpyrimidine **125** was converted into 4-hydroxy-2-methyl-5*H*-pyrrolo[3,2-*d*]pyrimidine-7-carbaldehyde **126**.[111] The first stage gives amidinium salt **127**, which is then formylated at the methyl group by the Vilsmeier reagent. The CH-acidity of the methylene group in intermediate **128** is enhanced, which facilitates heterocyclisation. The amidinium salt **127** does not cyclise when heated in DMF in the absence of $POCl_3$, which confirms the proposed mechanism.[111]



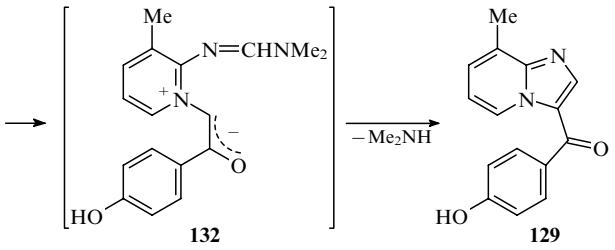
125 **127** **128** **126**

X = Cl, $OP(O)Cl_2$.

When hetarylamidines in which the pyridine nitrogen atom occupies an adjacent position to the amidine substituent are made to react with halo ketones, fused imidazole-containing heterocycles are produced. For example, 3-(4-hydroxybenzoyl)-8-methylimidazo[1,2-*a*]pyridine **129** was prepared by the reaction of N^1,N^1-dimethyl-N^2-(3-methylpyridin-2-yl)formamidine **130** with 2-bromomethyl 4-hydroxyphenyl ketone. In this process, the pyridine nitrogen atom is alkylated to give intermediate **131**. The high CH-acidity of the methylene group in this compound [112] ensures easy cyclisation, which proceeds *via* enolate anion **132**. Therefore, the basicity of the amidine substituent is normally sufficient for the subsequent transformations.



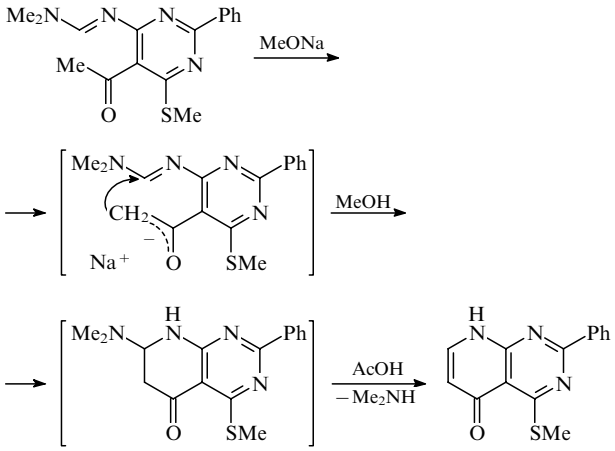
130 **131**



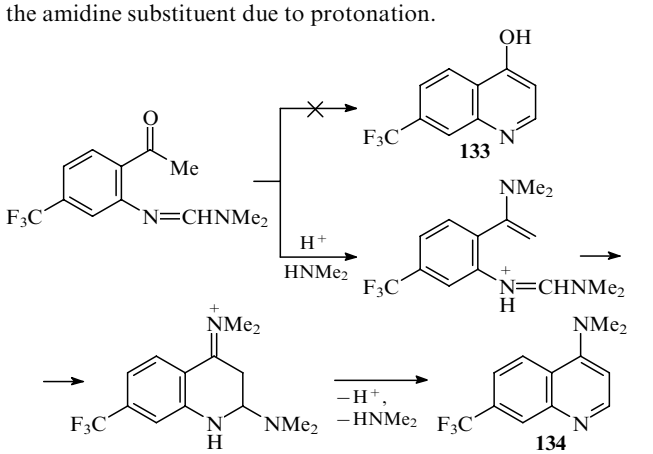
132 **129**

Despite the ambident properties of the enolate anion **132**, the process follows only the route involving the attack of the C-nucleophile on the electron-deficient formamidine centre; after elimination of dimethylamine, this results in the formation of a fused imidazole ring. This reaction has been used to synthesise derivatives of imidazo[1,2-*a*]pyridine,[113] imidazo[1,2-*a*]pyrimidine,[114] imidazo[1,2-*b*]-1,2,4-triazine,[115] imidazo[2,1-*b*]thiazole,[116] imidazo[2,1-*b*]-1,3,4-thiadiazole, pyrrolo[1,2-*a*]imid-azole[117] and so on.

The enolate anion generated from hetarylamidines having an acetyl substituent in the position adjacent to the amidine fragment also acts as a C-nucleophile. Intramolecular heterocyclisation results in the annelation of a pyridone fragment.[118] For example, 4-methylthio-2-phenyl-5-oxo-8*H*-pyrido[2,3-*d*]pyrimidine was prepared from 5-acetyl-4-dimethylaminomethylideneamino-2-phenyl-6-thiomethylpyrimidine.

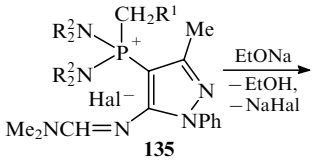


Cyclisation of 2-(3-methyl-1,3-diazabut-1-enyl)-4-trifluoromethylacetophenone yields 4-dimethylamino-7-trifluoromethylquinoline **134** instead of the expected 4-hydroxy-7-trifluoromethylquinoline **133**.[119] This unusual behaviour was explained by assuming that oxygen is replaced by dimethylamine at the stage of enolisation. The decrease in the nucleophilicity on passing from the enolate anion to enamine is counterbalanced, in the opinion of the authors, by the increase in the electrophilicity of the amidine substituent due to protonation.

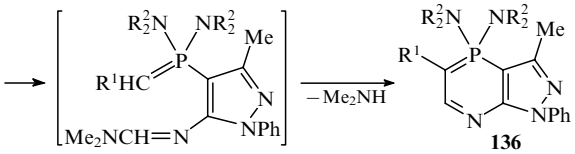


133 **134**

Phosphonium ylides generated from pyrazolylphosphonium salts **135** undergo intramolecular heterocyclisation *in situ* giving rise to pyrazolo[5,4-*b*]-1,4λ^5-azaphosphinines **136**.[76, 78, 120] 4-Nitrobenzylphosphonium salts cyclise much more easily than methylphosphonium salts because of their higher CH-acidity.



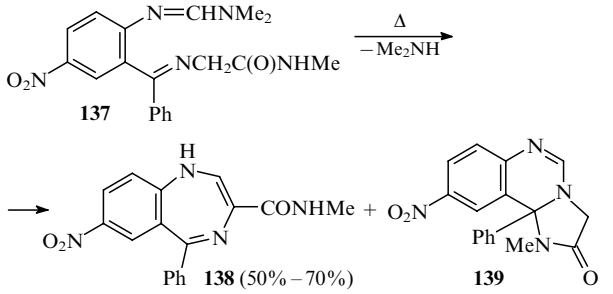
135



136

R^1 = H, Hal = I; R^1 = 4-$NO_2C_6H_4$, Hal = Br; NR_2^2 = N O, NEt_2.

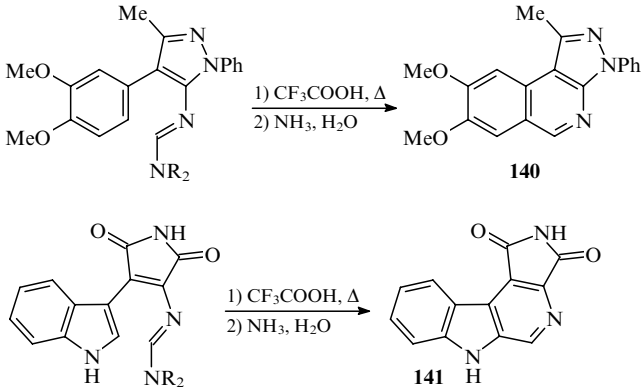
Heating of *N*-methyl-(2-dimethylaminomethylideneamino-5-nitrophenyl)-phenylmethylideneaminoacetamide **137** gives 3-methylaminocarbonyl-7-nitro-5-phenyl-1*H*-benzo[*e*]-1,4-diazepine **138** as the major product.[121] In the opinion of the authors, cyclisation occurs through the substitution of the enolate anion for the dimethylamino group.



137 **138** (50% – 70%) **139**

The side product, 1-methyl-9-nitro-10*b*-phenyl-1,10*b*-dihydroimidazo[1,2-*c*]quinazolin-2-one **139**, results apparently from an intramolecular cyclisation of the aza-Cope type of the product of rearrangement of the initial compound **137**.

The electrophilicity of the amidine substituent markedly increases upon protonation. This was used to synthesise 7,8-dimethoxy-1-methyl-3-phenylpyrazolo-[3,4-*c*]isoquinoline **140** and 6*H*-pyrrolo[3,4-*c*]*b*-carboline-1,3-dione **141** from the corresponding formamidines.[122, 123] Cyclisation occurs upon refluxing in trifluoroacetic acid over a period of 8 – 12 h.

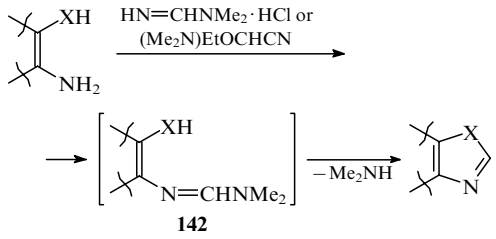


140 **141**

NR_2 = N O.

3. Reactions involving O- and S-nucleophiles

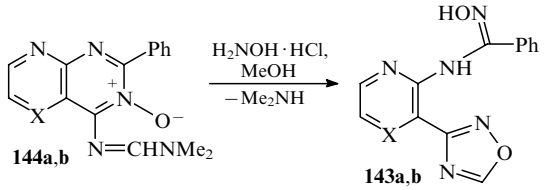
N,*N*-Dimethylformamidine hydrochloride and dimethylaminoethoxyacetonitrile are mild reagents used to transform the amino group into the amidine group. However, when they were made to react with 1,2-hydroxyamino or 1,2-sulfanylamino compounds, no amidines were produced; only cyclisation products — annelated oxazoles or thiazoles — were isolated instead. The formation of functionalised amidine intermediates **142** in these reactions was just postulated.[2] Aminophenols, aminobenzenethiols or the corresponding pyrimidine and pyridazine derivatives were used as the initial compounds.



142

X = O, S.

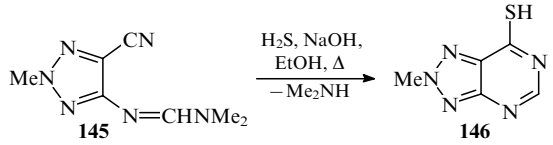
The systems containing an *N*-oxide fragment in the adjacent position to the amidine substituent are more stable; however, they undergo recyclisation on heating or on treatment with hydroxylamine salts.[124, 125] For example, *N*-hydroxy-*N*′-(1,2,4-oxadiazol-3-ylpyridin-2-yl)benzamidines **143a** and *N*-hydroxy-*N*′-(1,2,4-oxadiazol-3-ylpyridazin-2-yl)benzamidines **143b** were prepared from the corresponding formamidines **144a**,**b**.



144a,**b** **143a**,**b**

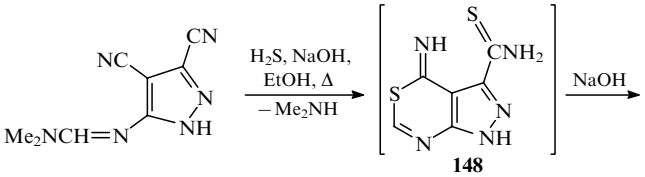
X = CH (**a**), N (**b**).

Treatment of hetarylformamidines containing a nitrile group next to the amidine group with hydrogen sulfide in the presence of bases is used to furnish a pyrimidinethiol fragment.[126] This method was used, for example, to transform 5-cyano-4-dimethylaminomethylideneamino-2-methyl-2*H*-1,2,3-triazole **145** into 2-methyl-7-thioxo-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine **146**.

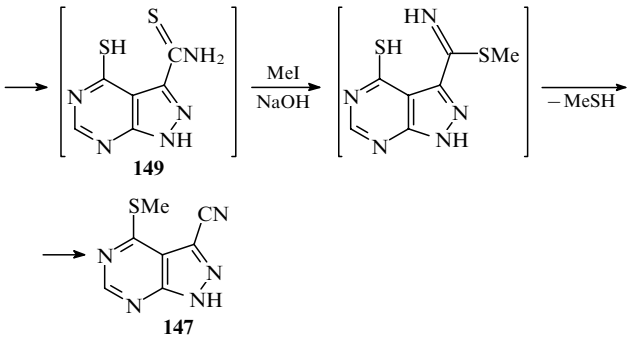


145 **146**

A similar reaction was used [66] in the synthesis of 3-cyano-4-methylthiopyrazolo[3,4-*d*]pyrimidine **147** from 3,4-dicyano-5-dimethylaminomethylideneamino-1*H*-pyrazole. It was suggested that 4-imino-3-thiocarbamoyl-1,4-dihydropyrazolo[3,4-*d*]-1,3-thiazine **148** undergoes the Dimroth rearrangement to give intermediate **149**. The compound **149** reacts with MeI to give the reaction product **147**.



148

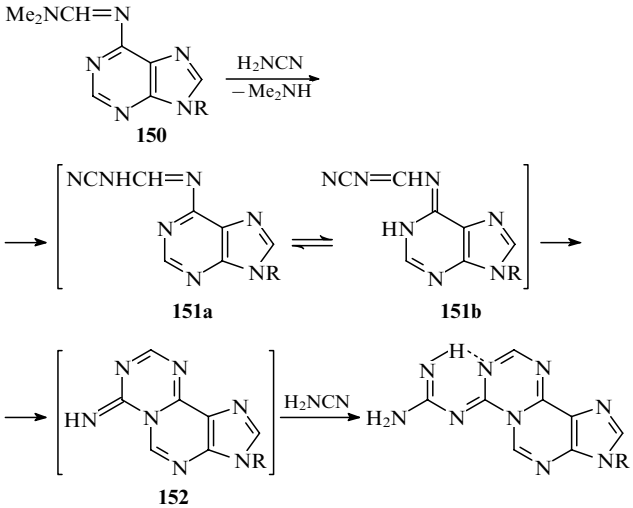


149 **147**

IV. Other heterocyclisation reactions

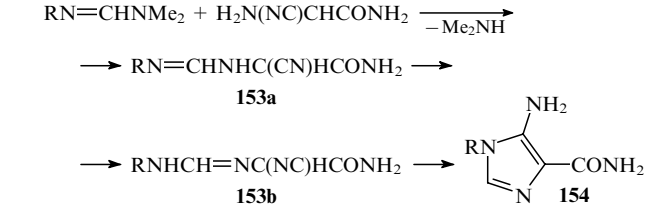
This Section surveys transformations of different types in which nucleophilic substitution at the formamidine carbon atom or cycloaddition involving the C = N fragment are not the key stages in the synthesis of heterocyclic compounds. The leading role in these reactions is played by polyfunctional reagents which react with the amidine or by transformations of the heterocyclic fragment of *N*-hetarylformamidines.

In the general case, during cyclisation of trisubstituted aryl- and hetarylformamidines with functionalised nitriles, first, the amidine amino group is replaced and subsequently N-nucleophilic heterocyclisation occurs. Thus the reaction of 6-dimethylaminomethylideneamino-9*H*-purine **150** with cyanamide starts with substitution of cyanamide for the dimethylamino group to give derivative **151a**; heterocyclisation resulting in 3-substituted 7-imino-3*H*-1,3,5-triazino[2,1-*i*]purine **152** occurs in the tautomer **151b**. The compound **152** reacts *in situ* with excess cyanamide to be converted into 7-amidinoimino-3*H*-1,3,5-triazino[2,1-*i*]purine.[127]



150 **151a** **151b** **152**

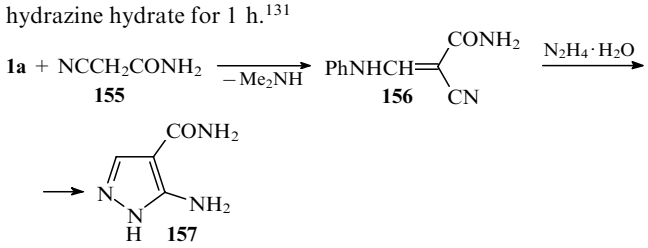
Trisubstituted formamidines react with aminocyanoacetamide according to the transamination pattern. The resulting *N*,*N*′-disubstituted amidines **153a** are equilibrated with their tautomers **153b**; the latter undergo cyclisation to give imidazole derivatives **154** due to the reaction between the NH and CN groups.[128] This strategy has also been employed in the synthesis of purine derivatives.[129, 130]



153a **153b** **154**

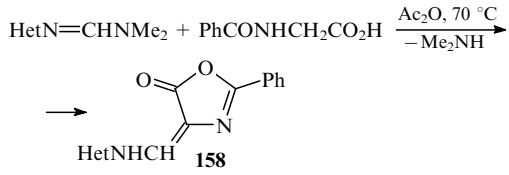
R = Ph (**1a**), Bn.

Highly basic N^1,N^1-dimethyl-N^2-phenylformamidine **1a** performs two functions in the reaction with cyanoacetamide **155;** first, it facilitates the transformation of cyanoacetamide into the carbanion on heating, and, second, it acts as the substrate in which this carbanion substitutes the dimethylamino group. The reaction yields 3-anilino-2-cyanoacrylamide **156**, which is converted into pyrazole derivative **157** on refluxing in an aqueous solution of hydrazine hydrate for 1 h.[131]

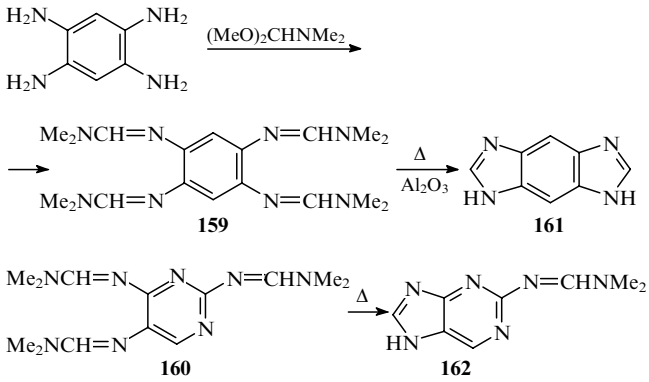


In this reaction, the amidine, like triethyl orthoformate, acts as a one-carbon synthon for the synthesis of pyrazole derivatives.

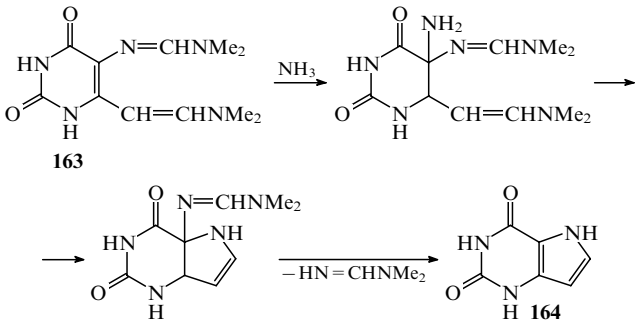
When *N*-hetarylformamidines are heated with hippuric acid in acetic anhydride, nucleophilic substitution at the formamidine carbon atom is accompanied by heterocyclisation. This reaction has been performed for pyridine, pyrimidine, pyrazine, pyridazine, oxazole and benzo-2,1,3-thiadiazole derivatives.[132] Compounds of the type **158** are the key intermediates in the synthesis of β-hetarylamino-α,β-dehydro-α-amino acids.[133–136]



Aromatic or heteroaromatic compounds containing more than two electron-donating substituents in the ring, including 1,2-diamino derivatives, behave unusually when made to react with dimethylformamide dimethyl acetal. These reactions can give bis- or even tetrakis-amidines, instead of fused imidazoles, for example, 1,2,4,5-tetrakis(dimethylaminomethylideneamino)benzene **159** and 2,4,5-tris(dimethylaminomethylideneamino)benzene **160**. Apparently, the [2-aminoaryl(hetaryl)]amidines formed initially cannot undergo cyclisation because of the low electrophilicity of the formamidine carbon atom. The corresponding fused imidazole-containing heterocyclic compounds — benzo[1,2-*d*;4,5-*d*′]diimidazole **161** and 2-dimethylaminomethylideneaminopurine **162** — can be prepared by subsequent pyrolysis in the presence of Al_2O_3 or on heating in diethylene glycol.[137,138]

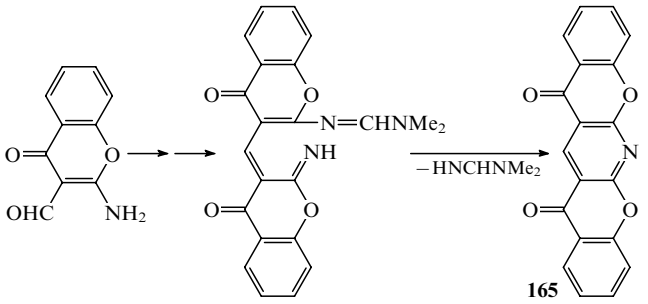


The amidine substituent can also function as a leaving group in heterocyclisation. Thus 5-dimethylaminomethylideneamino-6-(2-dimethylaminovinyl)pyrimidine-2,4-dione **163** is converted into pyrrolo[3,2-*d*]pyrimidine-5,7-dione **164** on treatment with ammonia.[139]

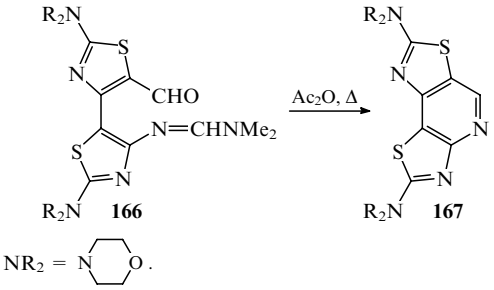


According to this scheme, ammonia adds to the double bond of the heterocycle, being attached to the more electrophilic carbon atom at the α-position relative to the carbonyl group.

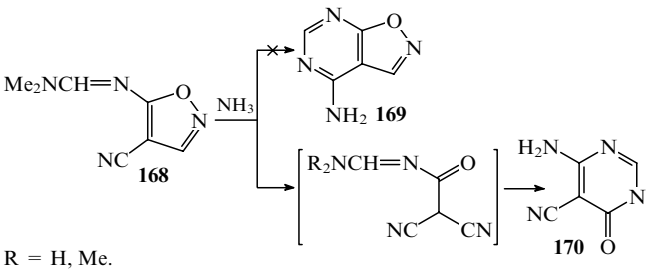
A similar transformation has been used to prepare 5,7-dioxa-6-aza-12,14-dione **165** from 2-amino-4-oxo-4*H*-chromenyl-3-carbaldehyde.[140]



Partial deamidination occurs during the cyclisation of 4′-dimethylaminomethylideneamino-2,2′-dimorpholino-5-formyl-[4,5′]bithiazole **166**, giving rise to 2,7-dimorpholinothiazolo[4,5-*b*]thiazolo[4,5-*d*]pyrimidine **167**.[141]

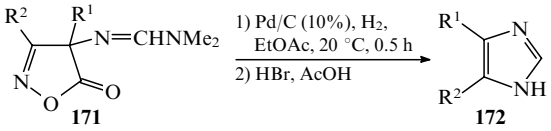


The ease of cleavage of the isoxazole ring at the N–O bond on treatment with nucleophiles or upon reduction accounts for the non-classical behaviour of isoxazolylamidines under heterocyclisation conditions. For example, when 4-cyano-5-dimethylaminomethylideneaminoisoxazole **168** is treated with a hot aqueous solution of ammonia, instead of the expected formation of 4-aminoisoxazolo[5,4-*d*]pyrimidine **169** or hydrolysis of the amidine substituent, recyclisation occurs giving rise to 4-amino-5-cyanopyrimidin-6-one **170**.[142]



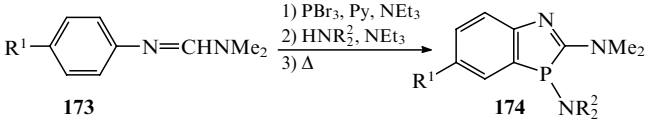
R = H, Me.

The reduction of 4-dimethylaminomethylideneaminoisoxazol-5-ones **171** catalysed by palladium supported on carbon affords imidazoles **172** in high yields[143] (90–95%). The key stage of the heterocyclisation is apparently intramolecular transamination at the formamidine carbon atom by the iminocarbonyl function, resulting from reduction of the N–O bond.



171 **172**

Formamidines react with trivalent phosphorus halides in the presence of bases to give molecules with a phosphorus–formamidine carbon bond.[144, 145] This approach has been used to synthesise phosphorus-containing heterocyclic compounds. For example, treatment of N^1,N^1-dimethyl-N^2-arylformamidines **173** with PBr_3 in the presence of bases followed by treatment with secondary amines and heating affords 3*H*-benzaazaphospholes **174**.[146, 147]



173 **174**

R^1 = Me_2N, MeO, Me, H, Br; R^2 = Me, Et, Pr^i.

V. Conclusion

The data considered here, which are concerned with heterocyclisation of N^1,N^1-disubstituted N^2-aryl- and N^2-hetarylformamidines, clearly demonstrate the high synthetic potential of these compounds and the prospects for using them to synthesise various heterocyclic systems, including those difficult to prepare otherwise.

However, it should be noted that the synthetic capacities of these compounds are far from being exhausted. The diverse reactivity of amidines is determined by the electrophilicity of the amidine carbon atom, the strong electron-donating ability of the amidine substituent, and the possibility of being involved in nucleophilic reactions and in pericyclic reactions of various types. In general, this allows not only annelation of five-, six- or seven-membered heterocycles to the rings present initially but also one-stage preparation of their functional derivatives by varying the functional substituents in the initial amidines, the reaction conditions and the reagents used for cyclisation.

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