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# NUCLEOPHILIC SUBSTITUTION OF HYDROGEN ATOMS IN THE PYRIDAZINE SERIES*. (REVIEW)

**A. F. Pozharskii and A. V. Gulevskaya**

*Information has been generalized on the nucleophilic substitution of hydrogen in monocyclic and condensed pyridazines, pyridazine N-oxides, and pyridazinium cations.*

**Keywords:** pyridazines, heteroaromatic nucleophilic substitution of hydrogen.

The investigation of nucleophilic aromatic substitution has more than a century of history. Traditionally most attention has been paid to substitution of facile leaving groups, such as Hal, $SO_3R$, $NO_2$, etc. Reactions of this type ($S_N^{ipso}$) are in many cases the main method of functionalizing a heterocycle [1]. Nucleophilic substitution of hydrogen ($S_NH$) is less widespread, primarily in view of the known instability of the hydride ion, which is formally a leaving group in these conversions. Meanwhile the $S_NH$ methodology in principle enables simplification of the synthesis of many heterocyclic compounds, releasing them from the need first to introduce a nucleophile into the hetero ring.

The first examples of $S_NH$ reactions, the amination and hydroxylation of heterocycles with sodium amide and solid anhydrous alkali respectively, were described by Chichibabin at the beginning of the twentieth century. They subsequently proved to have a large influence on the development of the chemistry of pyridine and other azines (see reviews [2-4]). However the need to use heterogeneous and extremely rigid conditions limited significantly the scope of the classical Chichibabin reaction. The most important achievement in this area remained the homogeneous oxidative amination of azines in the system $KNH_2$–$NH_3$–$KMnO_4$ proposed about 20 years ago by H. van der Plas (reviews [5, 6]). The use of potassium permanganate as an acceptor of hydride ion permitted working under exceptionally mild conditions and made possible the amination of substrates containing labile groups or simply groups unstable under the usual Chichibabin reaction conditions. It is curious that precisely this approach linked with the use of an external oxidizing agent in $S_NH$-amination reactions was developed by Bergstrom [7, 8] in the thirties of the twentieth century, but the inorganic nitrates proposed by him as oxidizing agents were not very convenient.

In difference to other azines little attention has been paid to the investigation of nucleophilic substitution of hydrogen in pyridazines for a long time. The first communication on pyridazines is dated 1886 [9], the chemistry of this class of compounds began to be developed intensively in the seventies of the twentieth century. Interest in pyridazines was restricted probably due to the circumstance that their aromatic derivatives are not found in nature. The discovery of biological activity in a series of pyridazine derivatives stimulated the vigorous growth of investigations in this area (for a review of the pharmacology of pyridazines see [10, 11]). The

* Dedicated to Professor E. Ya. Lukevics on the occasion of his 65th birthday.

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chemistry of pyridazine and its derivatives has been reviewed [12-20]. Some of the conversions discovered in recent years (such as the tandem $S_NH$ reaction), as it turned out, have no analogy in the azine series. In this case it seemed of interest to correlate all the existing information on reactions of the $S_NH$ type in monocyclic and condensed pyridazines.

In the present review conversions of neutral pyridazines and of activated systems based on them (pyridazine N-oxides and pyridazinium cations) are considered in order. Furthermore in the paper it emerged that certain $S_NH$ reactions proceed by a different mechanism, with the participation of not only anionic but also radical particles. Studies where only products of nucleophilic addition were isolated, but not of $S_NH$ substitution, are also cited, since the corresponding adducts, in principle, may readily be subjected to aromatization.

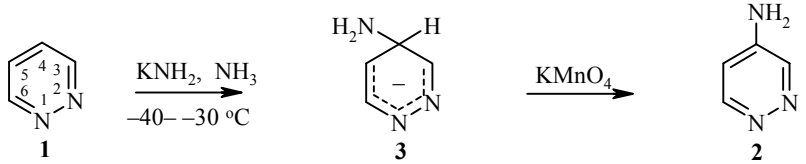
## 1. NUCLEOPHILIC SUBSTITUTION OF HYDROGEN ATOMS IN NEUTRAL PYRIDAZINES

In the pyridazine molecule each carbon atom is a subject to the action of two opposing forces, *viz*. the electron-withdrawing effect of the nitrogen atom in the *ortho* or *para* position conjugated with it and the weak electron-donating effect (due to the reorganization of the π-cloud) of the *meta* nitrogen atom. A characteristic feature of the π-electron distribution in pyridazine is the presence of a moderate positive π-charge on all the ring carbon atoms [21].

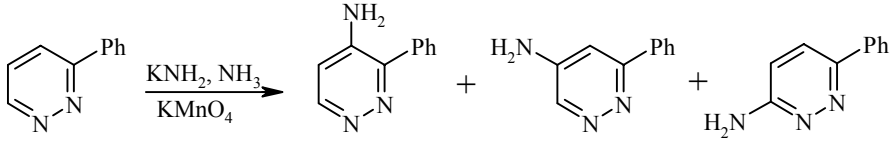
A characteristic of the disposition of the heteroatoms in the pyridazine molecule is that intermediates formed by the addition of nucleophiles to any of the carbon atoms are always stabilized by resonance. The energies of nucleophilic localization for $C_{(4)}$ and $C_{(3)}$ σ-complexes are comparable (2.35 and 2.36 β respectively). However in the majority of cases the $C_{(4)}$ atom in the pyridazine molecule undergoes nucleophilic attack.

### 1.1. Interaction with N-Nucleophiles

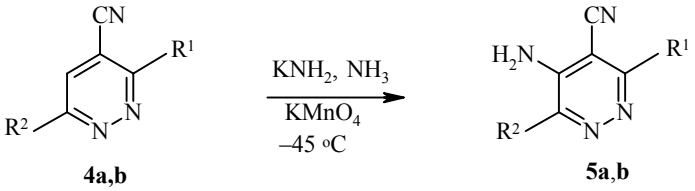
**1.1.1. Oxidative amination.** Pyridazine (**1**) undergoes oxidative amination on treatment with potassium amide in liquid ammonia in the presence of $KMnO_4$ forming the 4-amino derivative **2** in 92% yield [22]. The reaction proceeds by the classical $Ad_E$ mechanism. The intermediate dihydro adduct **3** was identified by low temperature NMR [23]. In the absence of potassium amide, i.e. under the action of ammonia itself, the reaction does not proceed, although in the case of other more π-deficient azines such reaction is possible.




A mixture of 4-, 5-, and 6-amino derivatives is formed from 3-phenylpyridazine under analogous conditions in yields of 49, 18, and 5% respectively [22].



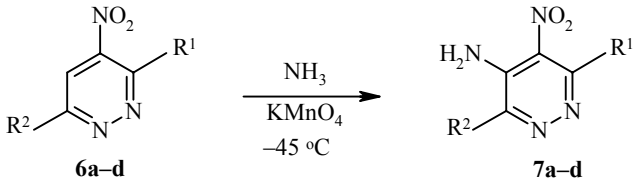
The selective formation of 4-aminopyridazines is observed on amination of 3-methoxypyridazines [22]. When a substituent is present in position 4 the nucleophile attacks the $C_{(5)}$ atom. For example, in the system $KNH_2$–$NH_3$–$KMnO_4$ the 4-cyanopyridazines **4a,b** are converted into amines **5a,b** in low yield (24 and 45% respectively) [24].




**4a,b** **5a**,**b**

**4, 5 a** $R^1$ = H, $R^2$ = Ph, **b** $R^1$ = $R^2$ = pyridyl-2

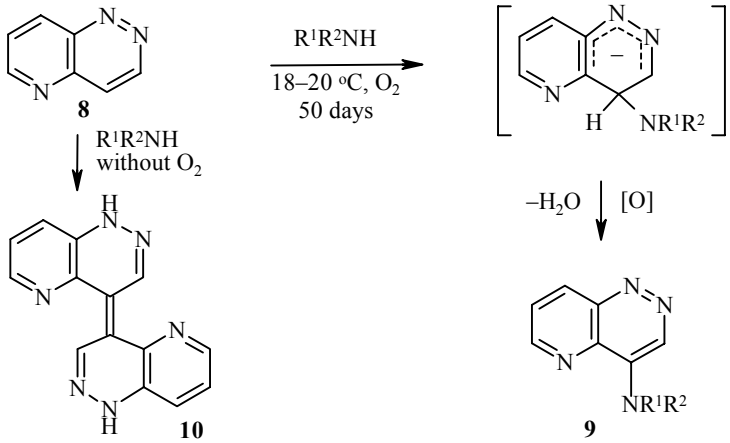
The 4-nitro group in pyridazines **6a-d** facilitates oxidative amination significantly, enabling it to proceed even in the absence of potassium amide [24]. It is evident that under conditions of kinetic control the limiting step is addition of ammonia. Products **7a-c** were obtained in yields of 93-98%. The unsubstituted 4-nitropyridazine **6d**, existing only in ether solution, forms an amination product **7d** in 18% yield, which is probably linked to its instability [24].




**6a–d** **7a–d**

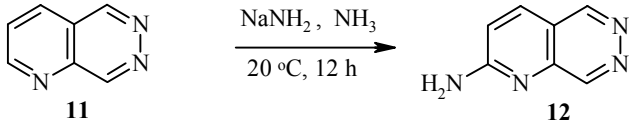
**6**, **7 a** $R^1$ = H, $R^2$ = Ph; **b** $R^1$ = $R^2$ = pyridyl-2; **c** $R^1$ = H, $R^2$ = 4-$MeOC_6H_4$; **d** $R^1$ = $R^2$ = H

There are no communications in the literature on the oxidative amination of condensed pyridazines, phthalazine and cinnoline in particular, in the $KNH_2$–$NH_3$–$KMnO_4$ system. However there is information on alkylamination. The 4-alkylamino derivatives **9** are formed on extended interaction of 5-azacinnoline (**8**) with alkylamines. Presumably oxygen from the air acts as oxidizing agent for the σ-complex (water was detected in the reaction mixture by GLC in an amount equivalent to the product formed) [25]. In the absence of available air the main reaction product was the dimer **10**. Compound **8** reacts slowly with amines possessing a reduced basicity, such as benzylamine, and the substitution products in this case were successfully obtained only on heating and adding an oxidizing agent such as $K_3Fe(CN)_6$. Azacinnoline **8** does not form amination products with arylamines and ammonia.



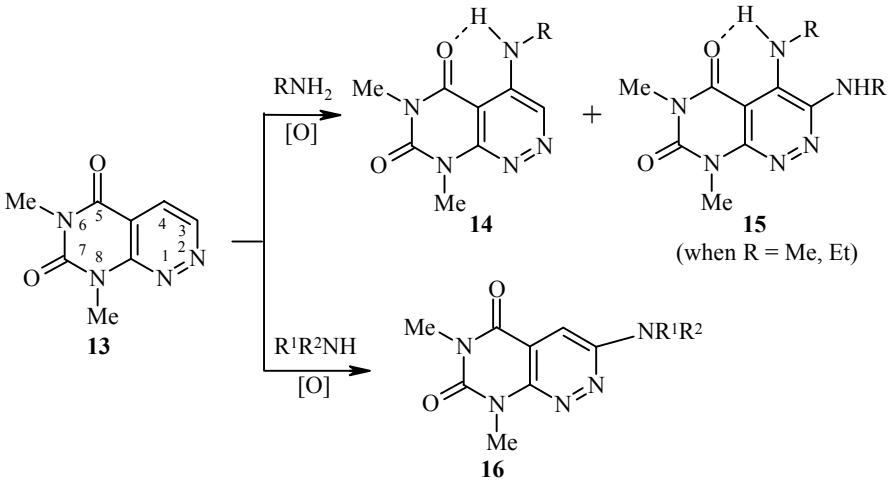

$R^1$ $R^2$ (yield, %): H, Me (70); H, *n*-Bu (95); H, *i*-Pr (30); H, *s*-Bu (20); Me, Me (20); Et, Et (<5); H, $(CH_2)_5N$ (50); $(CH_2)_5N$ (75); $(CH_2)_4N$ (95)

It is interesting that pyrido[2,3-*d*]pyridazine (**11**), which is an isomer of compound **8**, is aminated by the action of sodium amide in liquid ammonia (20°C, 12 h) in the pyridine ring, forming amine **12** in 38% yield [26].




**11** **12**

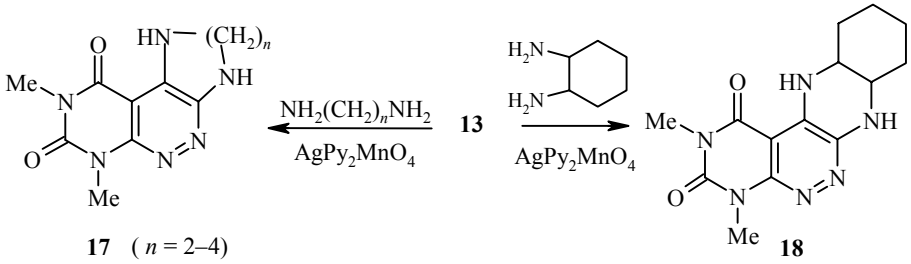
6,8-Dimethylpyrimido[4,5-*c*]pyridazine-5,7(6H,8H)-dione (**13**) displays a remarkable ability towards mono and di *ortho* substitution on reaction with aminating agents. Compound **13** reacts with an excess of liquid ammonia and primary alkylamines in the presence of $KMnO_4$ or the complex $AgPy_2MnO_4$ at -78 to 20°C (depending on the boiling point of the amine) forming 4-amino derivatives **14** in 53-90% yield. On interaction with methyl- and ethylamine the 3,4-diaminopyridazines **15** (about 10%) were obtained in addition to the monoamines **14**. Reaction with secondary amines (dimethylamine, piperidine, morpholine) proceeds under the same conditions with far more difficulty. The only products successfully isolated in this case are the 3-amino derivatives **16** (5-13% yield) and a large proportion of the starting material remains unchanged [27].




**13** **14** **15** (when R = Me, Et) **16**

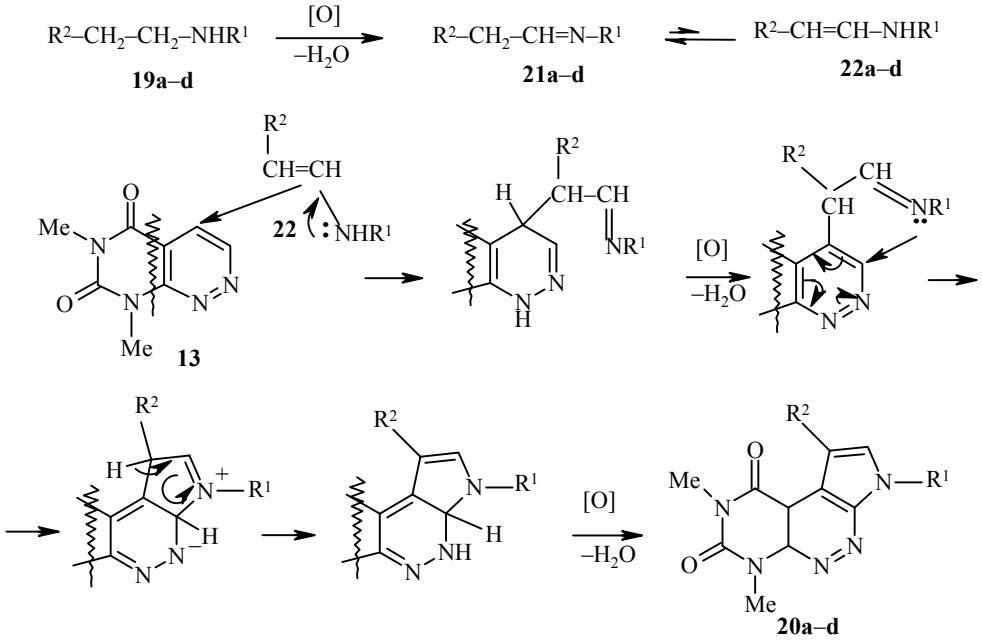
**14** R = H, Me, Et, Pr, *i*-Pr, *i*-Bu, *t*-Bu, $PhCH_2$, $C_6H_{11}$ (*cyclo*)-; **15** R = Me, Et;
**16** $R^1 = R^2 = Me$, $R^1R^2 = (CH_2)_5$, $(CH_2)_2O(CH_2)_2$

The pyridazinouracil **13** takes part in tandem nucleophilic substitution of hydrogen, which in many respects is caused by the presence in its pyridazine ring of two *ortho*-disposed electron-deficient carbon atoms. The products of the interaction of compound **13** with bifunctional nucleophiles (aliphatic α,ω-diamines) are the polycyclic compounds **17** and **18** [28].




**17** ( $n$ = 2–4) **18**

The interaction of pyridazinouracil **13** with diethyl-, dipropyl-, dibutyl-, and methylpropylamines **19a-d** in the presence of an oxidizing agent unexpectedly leads to annelation of a pyrrole nucleus and the formation of 6,8-dimethylpyrrolo[2',3':3,4]pyridazino[6,5-*d*]pyrimidine-7,9(6H,8H)-diones (**20a-d**) [29]. The first stage of this conversion is presumably oxidation of the secondary amine **19a-d** into a Schiff's base **21a-d**, which then reacts with the **13** molecule through the equilibrium quantities of enamine **22a-d**. The process includes two sequential $S_NH$ reactions in which enamine **22** first plays the role of a C-nucleophile and then of an N-nucleophile and is developed according to the following scheme.



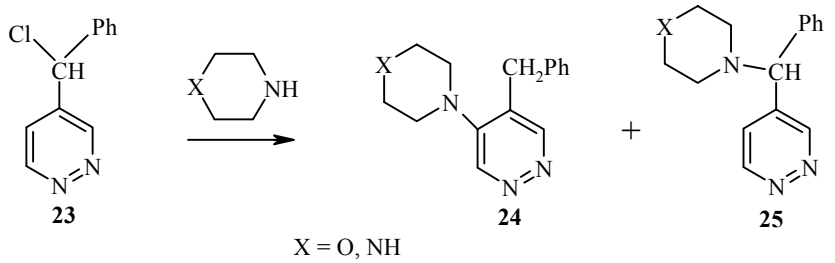

**19-22 a** $R^1$ = Et, $R^2$ = H; **b** $R^1$ = Pr, $R^2$ = Me; **c** $R^1$ = Bu, $R^2$ = Et; **d** $R^1$ = $R^2$ = Me

The mechanism of the **13**→**22** transformation is confirmed experimentally by the fact that compound **13** reacts with the azomethines **21a-f** (**e** $R^1$ = Pr, $R^2$ = H, **f** $R^1$ = Et, $R^2$ = Me) known to be obtained, with the formation of pyrroles **22a-f**.

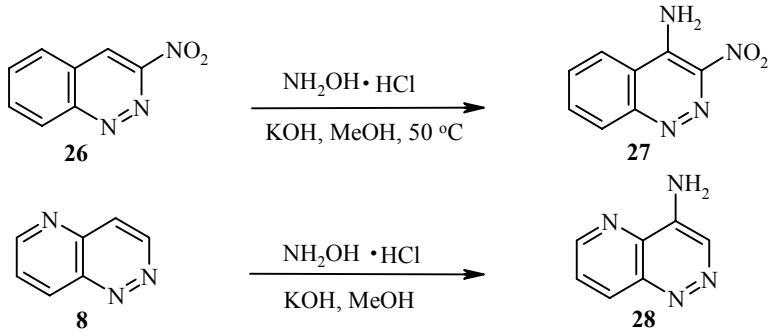
Until recently there was no information in the literature on nucleophilic substitution of hydrogen in cinnoline. We found [30] that, unlike 5-azacinnoline (**8**) and pyridazinouracil (**13**), cinnoline displays a low reactivity towards amines. It does not react with potassium amide in liquid ammonia, methyl-, benzyl-, and cyclohexylamines in the presence of an oxidizing agent ($KMnO_4$ or $AgPy_2MnO_4$). The reaction of cinnoline with ethylenediamine proceeds extremely slowly with the formation of 4,4'-biscinnolyl (2.5% yield) as the sole product. The reason for the low reactivity of cinnoline in the oxidative amination reaction may be its extremely low π-deficiency, comparable with the π-deficiency of pyridine [1], which is also not aminated in the $KNH_2$–$NH_3$–$KMnO_4$ system [6, 23].

**1.1.2. Vicarious nucleophilic substitution.** All the known vicarious nucleophilic substitutions of hydrogen (*VNS*) in the pyridazine series may be divided into two types: 1) reactions in which aromatization of the σ-adducts is realized by fission of a leaving group from the C-substituent of the substrate; 2) reactions in which the nucleophile contains a readily leaving group.

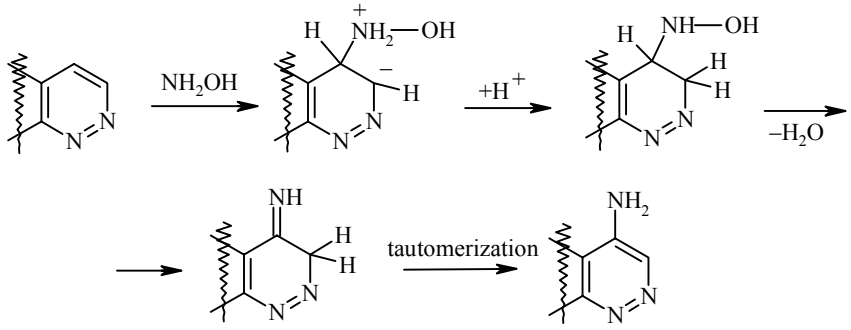
Examples of reactions of the first type are scarce. Thus on reacting pyridazine **23** with N-methylpiperidine or morpholine a mixture is formed of **24**, the product of the *VNS* reaction, and of **25**, the product of the nucleophilic substitution of chlorine [31].



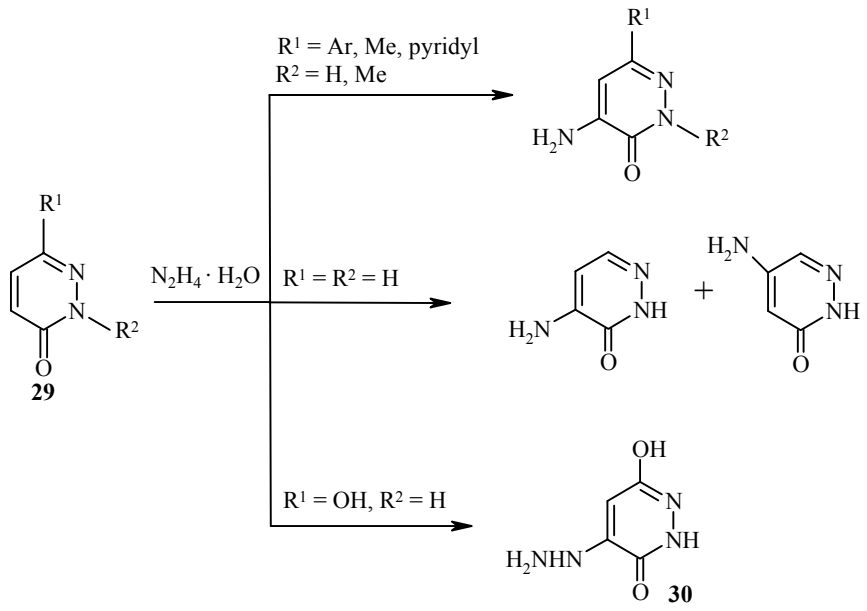

The interaction of 3-nitrocinnoline (**26**) or 5-azacinnoline (**8**) with hydroxylamine may serve as an example of *VNS* reactions of the other type. In difference to alkyl- and arylamines this proceeds readily even in the absence of oxidizing agent. The reaction products are the 4-amino derivatives **27** (62% yield) and **28** (>90% yield) [25,32].




It is evident that aromatization of the intermediate σ-complex occurs according to the following scheme.

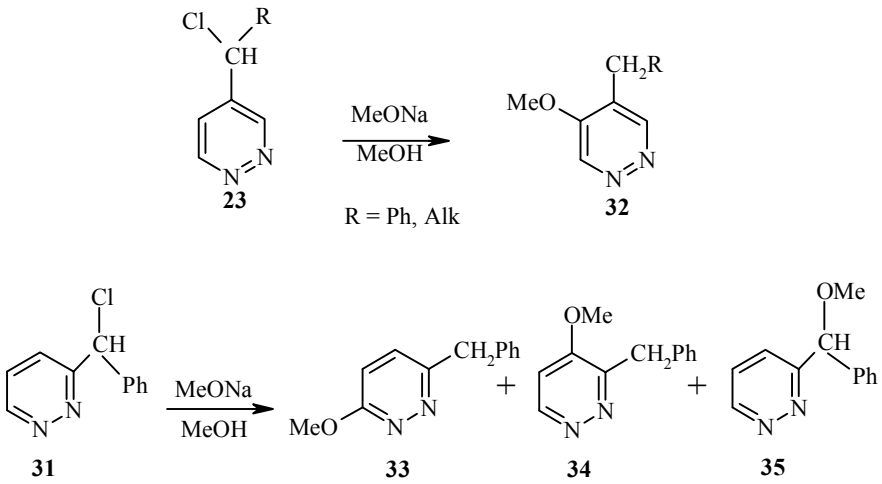



Pyridazinones **29** react with hydrazine hydrate in a similar way forming the corresponding products in 30-90% yield. A mixture of 4- and 5-amino derivatives was obtained from the unsubstituted pyridazine in yields of 14 and 24% respectively. In the case of maleic acid hydrazide (**29**, $R^1$ = OH, $R^2$ = H) probably a classical $S_N2$ Ar mechanism occurs and with the assistance of oxygen of the air the 4-hydrazino derivative **30** is formed (80% yield) [33, 34]. However the possibility is not excluded of the initial formation of 4-aminopyridazinone and subsequent substitution of the amino group by a hydrazine group (examples of such hydrazinolyses are known [35-37]).

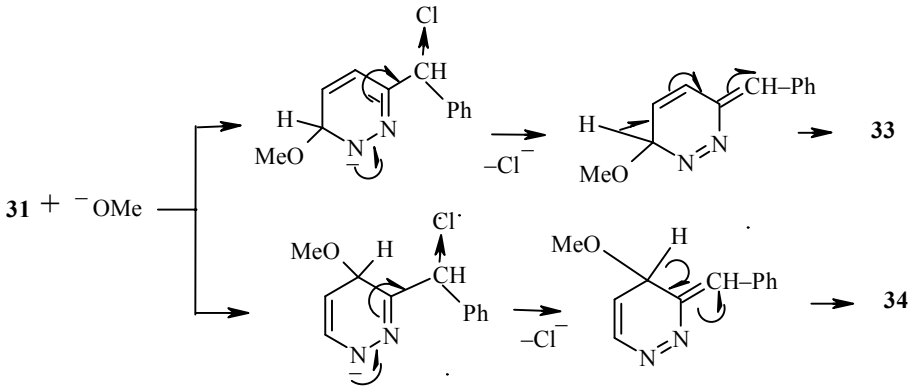



### 1.2. Interaction with O-Nucleophiles

Pyridazines **23** and **31** are subject preferentially to a vicarious nucleophilic substitution on reaction with sodium methylate in methanol [31, 38]. The reaction of 4-substituted compounds **23** with MeONa proceeds selectively with the formation of 5-methoxy derivatives **32** (about 50% yield), but in the case of the 2-substituted **31** a mixture was obtained of the 4- and 6-methoxy derivatives **33** and **34** (22 and 15% yields respectively) and 3-(α-methoxybenzyl)pyridazine **35** (19% yield) [38].

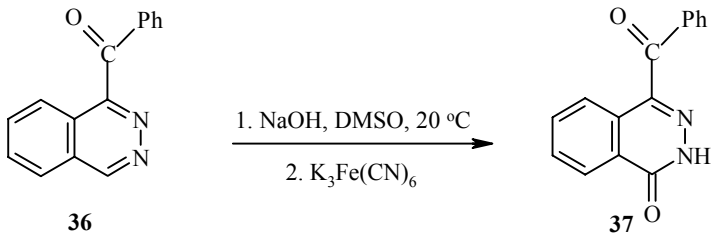



The scheme given below demonstrates the mechanism of formation of the products of *tele* substitution of **33** and **34**.



The interaction of compound **31** with sodium ethylate and sodium β-(dimethylamino)ethylate proceeds analogously [38], but on reaction with N- and S- nucleophiles or sodium phenolate, substitution of halogen by an $S_N2$ type of reaction takes place exclusively [39, 40].

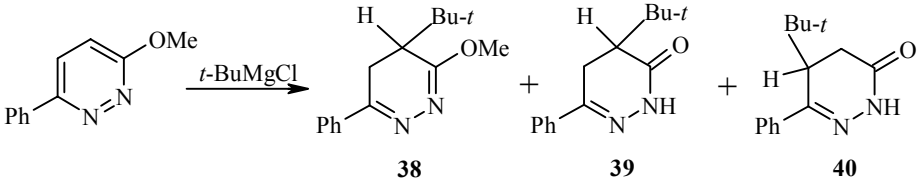
The oxidative hydroxylation of 1-benzoylphthalazine (**36**) with alkali in DMSO has been described, however the yield of the reaction product **37** was 23% overall [39].



## 1.3. Interaction with C-Nucleophiles

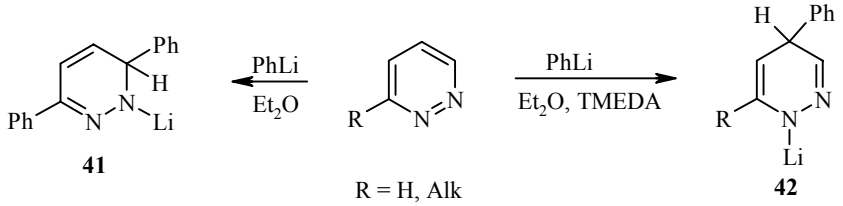
**1.3.1. Reactions with organometallic reagents.** Grignard reagents and organolithium compounds add to pyridazine with the formation of 1,4-adducts. The latter are capable of rearrangement into 1,2-dihydro derivatives [41-56].

4-*tert*-Butyl-3,6-dimethoxypyridazine is attacked by *tert*-butylmagnesium chloride at the $C_{(5)}$ atom and after treatment with water a mixture of *cis*- and *trans*-4,5-dihydro adducts is formed [53,54]. 4-*tert*-Butyl-3-methoxy-6-phenyl-4,5-dihydropyridazine (**38**) is formed preferentially from 3-methoxy-6-phenylpyridazine under the same conditions, together with the isomeric 4,5-dihydropyridazinones **39** and **40** [15].



3,6-Dimethoxypyridazine interacts with *tert*-butyllithium and *n*-butyllithium with the formation of the corresponding 4-substituted 4,5-dihydropyridazines [15].

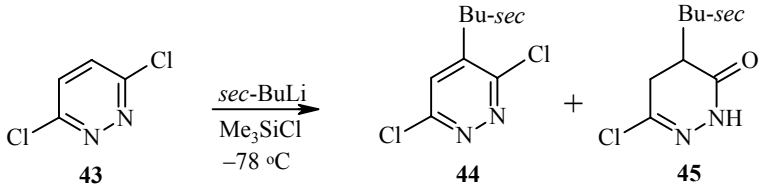
In difference to the examples given, pyridazine and 6-alkylpyridazines are converted by the action of phenyllithium in ether into addition products at the $C_{(3)}$ atom **41**, which is evidently linked with the preliminary coordination of PhLi at the $N_{(2)}$ aza group. Addition of N,N,N',N'-tetramethylethylenediamine enables the formation of the $C_{(4)}$ adduct **42** [47].




**41** **42**

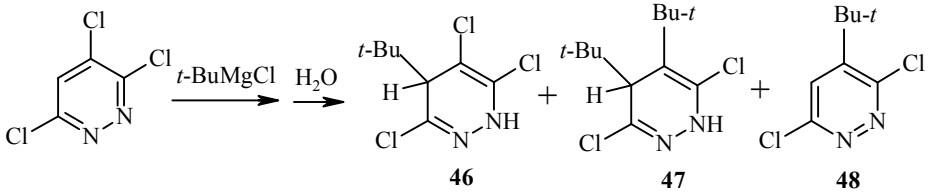
The nucleophilic addition to pyridazine of perfluoroalkyllithium reagents, generated *in situ* from perfluoroalkyl iodides and MeLi–LiBr in the presence of $BF_3 \cdot Et_2O$, occurs exclusively in the position *ortho* to the aza group [56].

1,4-Addition predominates in the case of chloropyridazines, but reaction takes place ambiguously. Thus 3,6-dichloropyridazine (**43**) reacts with *sec*-butyllithium in the presence of trimethylchlorosilane with the formation of the 4-*sec*-butyl derivative **44** and dihydropyridazinone **45** [52].



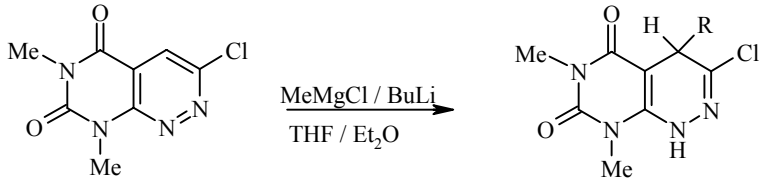

**43** **44** **45**

The interaction of 3,4,6-trichloropyridazine with *tert*-butylmagnesium chloride leads to a mixture of products **46-48** in which compounds **46** and **47** predominate [55].



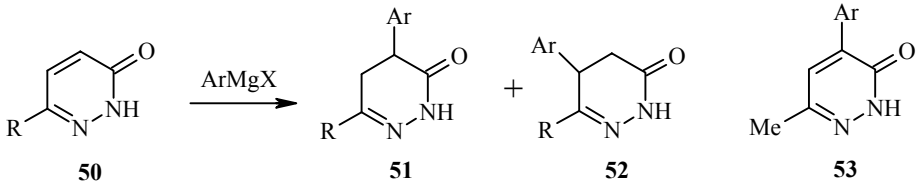

**46** **47** **48**

The $C_{(4)}$ atom in 3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6H,8H)-dione (**49**) is subject to nucleophilic attack (when R = Me the yield of product was 58%, when R = Bu yield was 21%) [48].




**49**

In 6-aryl(alkyl)pyridazinones **50** addition of Grignard reagents occurs at the $C_{(4)}$ or $C_{(5)}$ atoms with the formation of compounds **51** and **52** [43,49,51]. Their ratio depends on the reaction conditions. On using a mixture of THF and ether as a solvent the yields of products **51** and **52** were 16-35 and 3.5-11% respectively [43]. In a mixture of ether and benzene the 4-aryl derivative **51** is formed exclusively (55-91% yield) [49-51]. On carrying out the reaction in pure THF only pyridazinone **53** was obtained (33-45% yield) [43]. 6-Aryl-$N_{(2)}$-phenylpyridazin-3-ones react analogously with phenylmagnesium bromide [51].

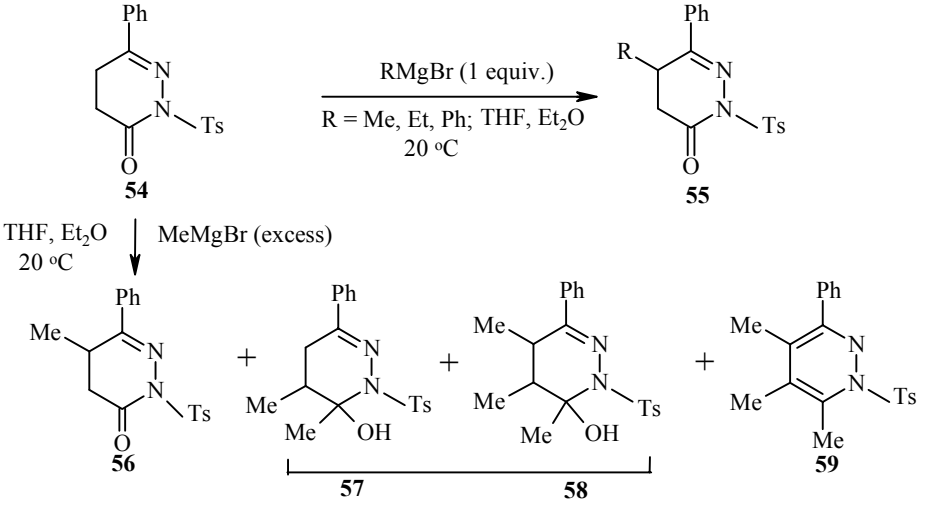


**50** **51** **52** **53**

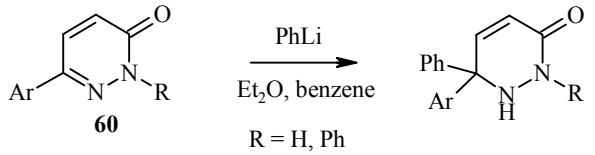
R = H, Me, Ph, 4-$MeOC_6H_4$, 4-$ClC_6H_4$, 4-$MeC_6H_4$; Ar = Ph, 4-$MeC_6H_4$, α-naphthyl

It was noted in [51] that the reaction of Grignard reagents with 5-phenylpyridazin-3(2H)-ones proceeds with difficulty and the $C_{(4)}$ adduct is formed in insignificant amount.

6-Phenyl-2-tosyl-3(2H)-pyridazinone (**54**) forms exclusively adducts **55** under the action of an equimolar amount of methyl-, ethyl-, or phenylmagnesium bromide. However with an excess of organometallic reagent a mixture is formed of the products of nucleophilic attack at the carbonyl group and at another ring carbon atoms. Thus treatment of compound **55** with an excess of methylmagnesium bromide leads to a mixture of compounds **56-59** (yields of products were **56** 14%, **57**, **58**, and **59** 30%) [50].



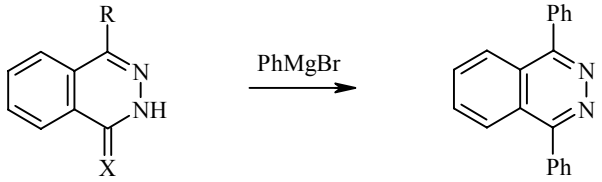
Products of addition at $C_{(6)}$ (64-91% yield) are obtained as a result of the interaction of 6-arylpyridazin-3-ones **60** and phenyllithium as in the case of pyridazines [49]. The activating effect of the aza group is greater than that of the carbonyl substituent in this case .



**60**

6-Aryl-2,4-diphenylpyridazin-3(2H)-ones react with an excess of PhLi or PhMgBr with the formation of 6-aryl-2,3,4,6-tetraphenyl-1,2,3,4-tetrahydropyridazines [49].

On interaction of PhMgBr with phthalazinones or phthalazinethiones **61** 1,4-diphenylphthalazine (**62**) is obtained, while the action of PhLi leads exclusively to 4-phenyl-3,4-dihydrophthalazin-1(2H)-ones (or thiones) [16].

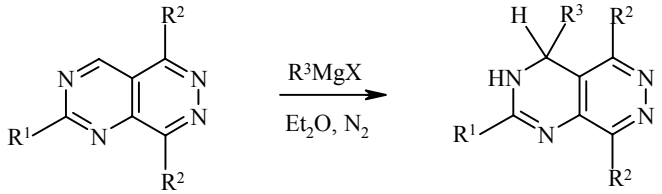



**61** **62**

**61** R = H, Ph, X = O, S

1-Substituted phthalazine $N_{(2)}$-oxides are subject to addition at $C_{(4)}$ under the action of organometallic reagents [16].

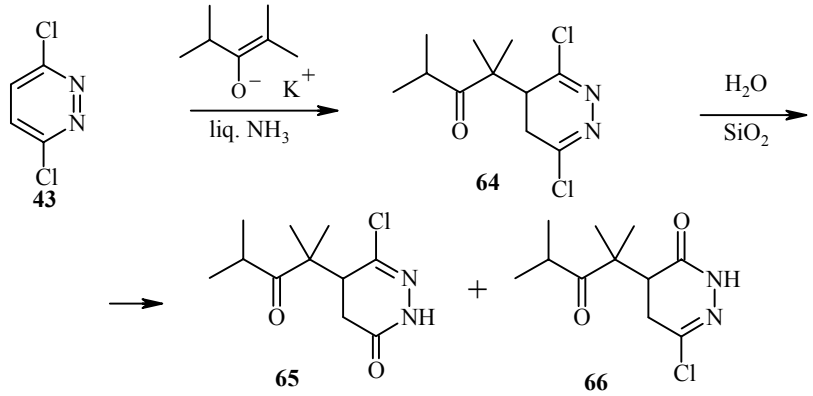
The pyrimidine ring in pyrimido[4,5-d]pyridazines **63** is the more reactive in relation to organomagnesium compounds [57].




**63**

$R^1$ = Me, Ph, 4-$MeC_6H_4$, $R^2$ = $(CH_2)_5N$–, $(CH_2)_2O(CH_2)_2N$, $R^3$ = Alk, Ar

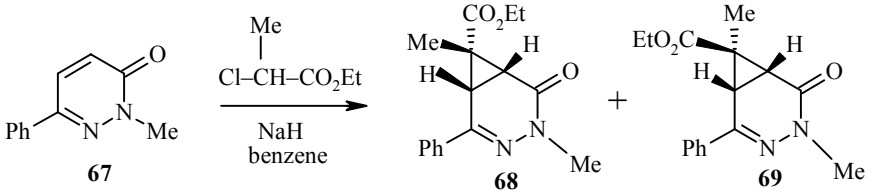
**1.3.2. Reactions with enolate and cyanide ions.** Examples have been described of the interaction of pyridazines with ambident nucleophiles, particularly enolates. 3,6-Dichloropyridazine (**43**) reacts with the potassium enolate of diisopropyl ketone in liquid ammonia with the formation of the unstable dihydro adduct **64**, which in the presence of moist silica gel is hydrolyzed to the isomeric chlorodihydropyridazinones **65** and **66** [58].




**43** **64** **65** **66**

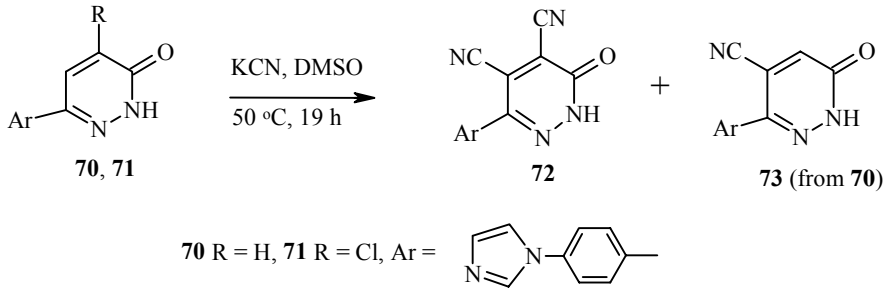
The reactivity of compound **43** in this case is not completely typical for haloheterenes in which halogen is more frequently substituted under these conditions [58].

By the action of 2-chloropropionic acid ethyl ester in the presence of sodium hydride pyridazinone **67** is subject to methylenation at the $C_{(4)}$=$C_{(5)}$ bond with the formation of the condensed stereoisomeric cyclopropanes **68** and **69** [59].




**67** **68** **69**

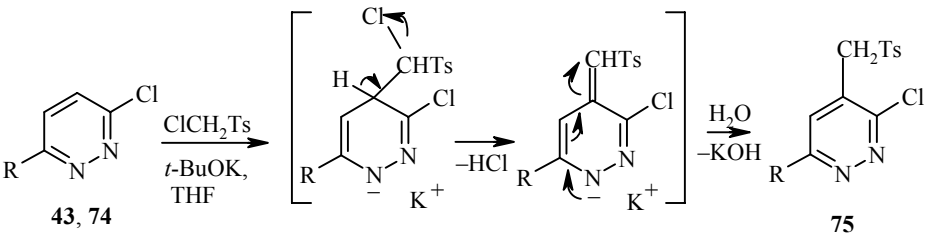
The 4,5-dicyano derivative **72** was isolated on interacting pyridazin-3-one **70** and its 4-chloro derivative **71** with KCN in DMSO. In the case of compound **70** the monocyano derivative **73** was formed in addition to the main product [60]. It is noted that this conversion proceeds more rapidly in the presence of oxygen and significantly more slowly in an inert atmosphere. On carrying out the reaction with $Cu(CN)_2$ or KCN in other solvents the cyanides **72** and **73** are not formed [60].




**70**, **71** → **72** + **73** (from **70**)

**70** R = H, **71** R = Cl, Ar =

**1.3.3.** ***VNS*** **reactions.** The reaction of 3-chloro- (**74**) and 3,6-dichloropyridazines (**43**) with tosylchloromethane in the presence of *t*-BuOK in THF leads to the formation of product **75** (37-98% yield), as a result of substitution not of the chlorine atom but of the hydrogen atom in the most electron-deficient position 4 [61]. It is evident that the role of nucleophile is played by the tosylchloromethyl carbanion generated *in situ*.

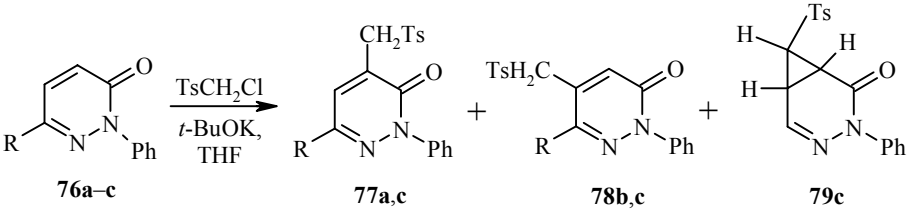



**43**, **74** → **75**

**43** R = Cl, **74** R = H

Unsubstituted pyridazine does not undergo a similar conversion, presumably due to its lower electrophilicity [61].

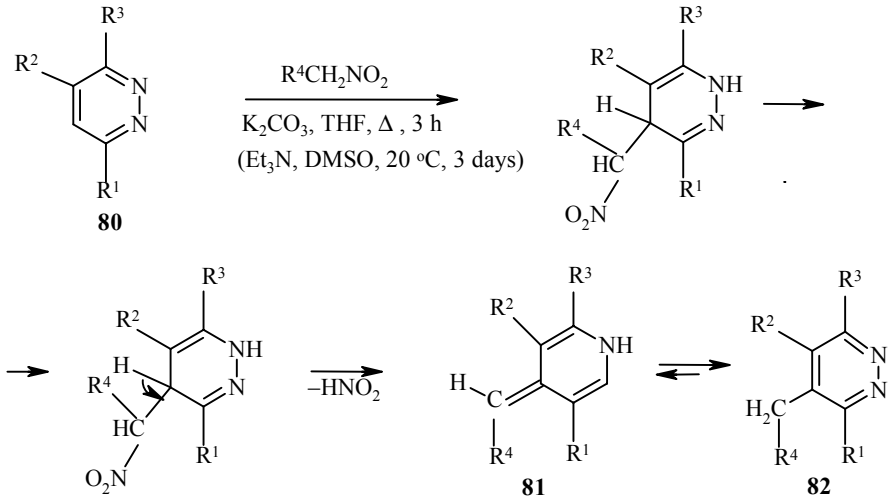
Under analogous conditions the 6-R-pyridazinones **76a,b** form 4- and 5-tosylmethyl derivatives **77a** and **78b** in high yield (93 and 88% respectively) [61]. For compound **76c** the reaction proceeds ambiguously and leads to a mixture of products **77c-79c** (26, 12, and 15% yields respectively) [61].




**76a–c** → **77a**,**c** + **78b**,**c** + **79c**

**76–78 a** R = Cl, **b** R = MeO, **c** R = H

The alkylation of pyridazine-3,6-diones with nitroalkanes in basic media has also been reported [61]. The interaction of pyridazines **80** with nitromethane or nitroethane in the presence of base leads to the corresponding 5-methyl- and 5-ethyl derivatives **82** (10-93% yield) [62].




**80**

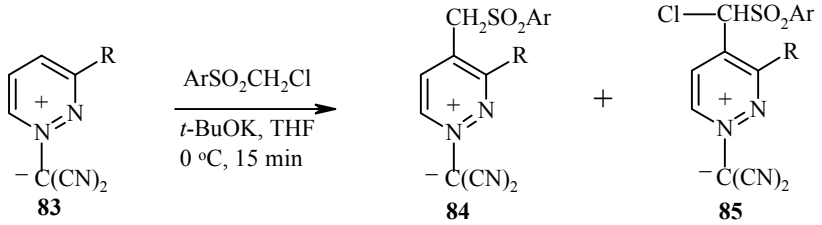
**81**

**82**

**80**, **81** $R^1 = CO_2Me$, $R^2 = R^3 =$ H, $R^4 = Me$; $R^1 = R^3 = Cl$, $R^2 = CN$, $R^4 = H$, Me

The 4-carboxy- and 4-ethoxycarbonylpyridazin-3(2H)-ones and the pyridazin-6(1H)-ones isomeric with them are alkylated in position 5 [62].

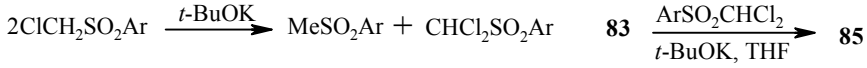
The dicyanomethyl ylides of pyridazinium **83** are convenient substrates for carrying out vicarious nucleophilic substitution. The *VNS* reaction here proceeds selectively at the $C_{(4)}$ atom even in the presence of a donor substituent in position 3 and leads to products **84** (14-75% yield) and **85** (0-70% yield) [63, 64].




**83** **84** **85**

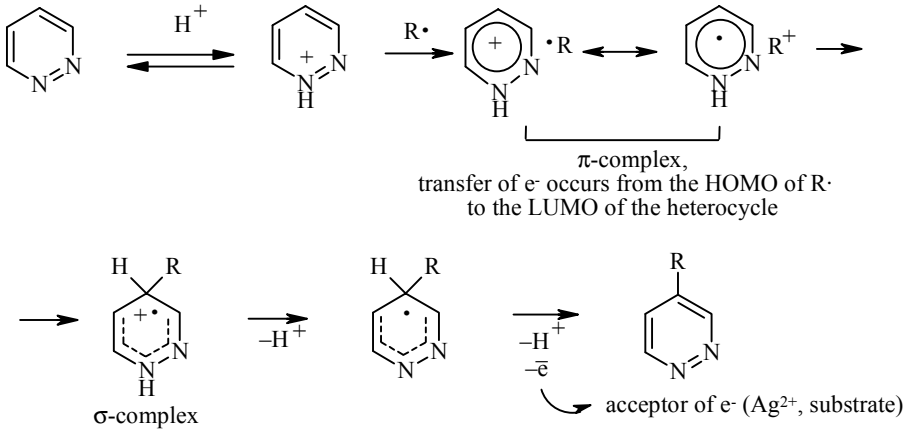
R = H, Me, MeO, EtO, Ph, $(CH_2)_5N$–; Ar = Ph, 4-$MeC_6H_4$

It is assumed that compound **85** is also the product of a vicarious nucleophilic substitution and is formed according to the following scheme [63, 64].




The ratio of compounds **84** and **85** depends on the substituent R. When R = H product **85** predominates, but when R = EtO or Ph it is generally not formed. The absence of substitution at the $C_{(6)}$ atom is explained by steric difficulties.

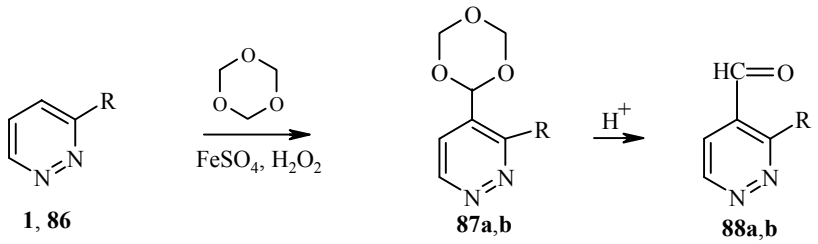
**1.3.4. Radical nucleophilic substitution.** As for the majority of π-deficient azines, pyridazines are subject to homolytic alkylation and acylation according to Minisci [65]. The reaction mechanism may be represented by the following scheme.



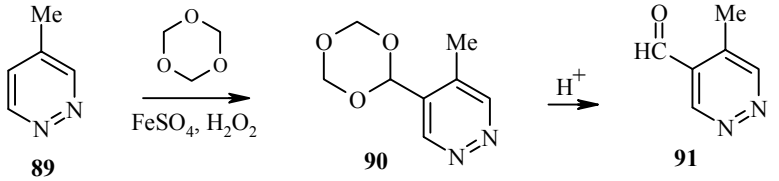

Alkyl radicals are generated by various methods but the most efficient are the oxidative decarboxylation of carboxylic acids by peroxybisulfate ions catalyzed by silver ions. Acyl radicals are obtained in the system RCHO–$FeSO_4$–*t*-BuOOH–$H_2SO_4$.

Alkyl and acyl radicals have a nucleophilic character, since they readily and extremely selectively react with azines in acidic media.

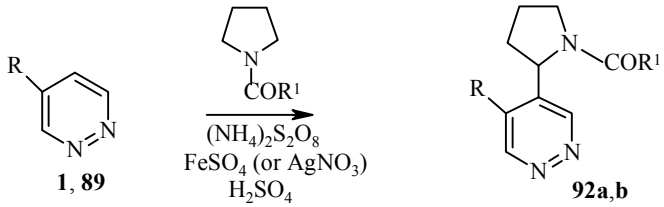
Reactions of pyridazines **1**, **86**, and **89** with *sym*-trioxanyl radicals generated from 1,3,5-trioxane by the action of Fenton's reagent ($FeSO_4$–$H_2O_2$) occurs exclusively at position 4(5) and is accompanied by the formation of trioxanyl derivatives **87** and **90**, the yield of which did not usually exceed 30% [66, 67]. Hydrolysis of compounds **87** and **90** gave the aldehydes **88** and **91** respectively.




**87a**, **88a** R = H; **86**, **87b**, **88b** R = Me



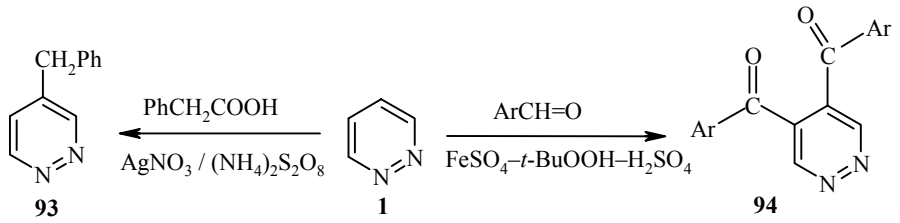

The interaction of pyridazine **1** and 4-methylpyridazine **89** with N-acyl-2-pyrrolidinyl radicals leads to the formation of compounds **92a,b** [17,68].




**92 a** R = H; **89**, **92b** R = Me

Under analogous conditions substitution of hydrogen at both the $C_{(4)}$ and $C_{(5)}$ atoms occurs in 3-methylpyridazine **86** [17].

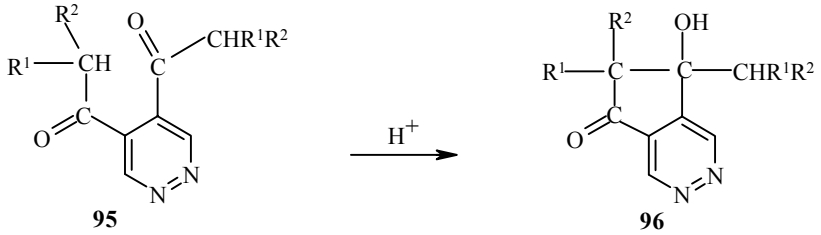
The interaction of pyridazines with methyl radicals generated from acetic acid is characterized by a low regioselectivity [74], on the other hand homolytic benzylation of pyridazine **1** leads exclusively to 4-benzylpyridazine **93** [69].



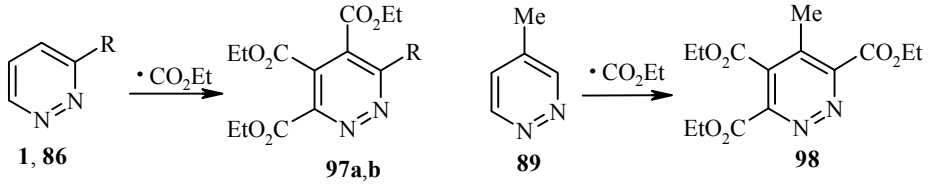

Ar = Ph; 4-$MeOC_6H_4$; 3,4-$Me_2C_6H_3$

Aroyl radicals also attack position 4(5) of pyridazine **1**. The diketones **94** were obtained in this way in 55-75% yield [69,70]. 4-Methyl- and 4-ethoxycarbonylpyridazines form 5-monoaroyl derivatives under the same conditions [71-73].

The reaction of pyridazine **1** with aliphatic acyl radicals leads to 4,5-diacyl derivatives **95** which are spontaneously subject to an intramolecular aldol condensation with the formation of cyclopenta[*d*]pyridazine **96** as the only reaction product [71].




The nucleophilic attack of the ethoxycarbonyl radical has little selectivity since the introduction of the acceptor $CO_2Et$ group into the pyridazine nucleus aids further nucleophilic substitution. The trisubstituted **97** and **98** are formed by the action of ethyl pyruvate on pyridazine **1**, and on 3-, and 4-methylpyridazines **86** and **89** under the conditions of the Minisci reaction [75].



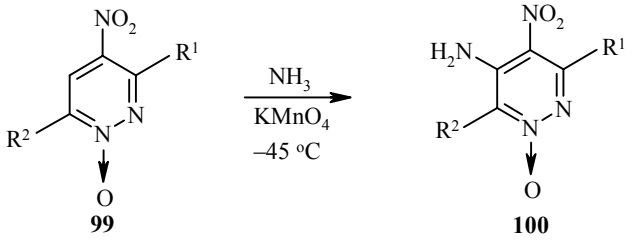

**97 a** R = H, **b** R = Me

In the two-phase system $H_2O$–$CH_2Cl_2$ 4-alkylpyridazines are subject to monosubstitution at the $C_{(5)}$ atom [75,76], pyridazine **1** and 3-methylpyridazine **86** form 4,5-pyridazinedicarboxylates [76].

## 2. NUCLEOPHILIC SUBSTITUTION OF HYDROGEN ATOMS IN PYRIDAZINE N-OXIDES

### 2.1. Classical Addition–Cleavage Reactions ($S_N2$ Ar)

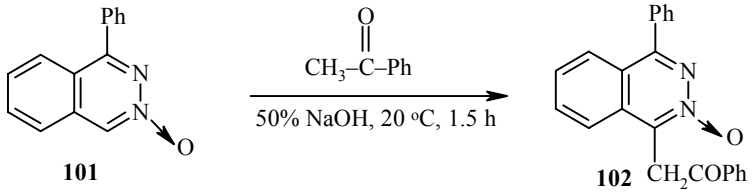
The interaction of 4-nitropyridazine $N_{(1)}$-oxides **99** with ammonia and $KMnO_4$ leads to 5-aminopyridazine **100**, yields of which were 50-75% [77]. The N-oxide group does not take an obvious part in the reaction and remains unchanged.




**99** **100**

**99**, **100** $R^1$, $R^2$ = H, Ph, MeS, MeO

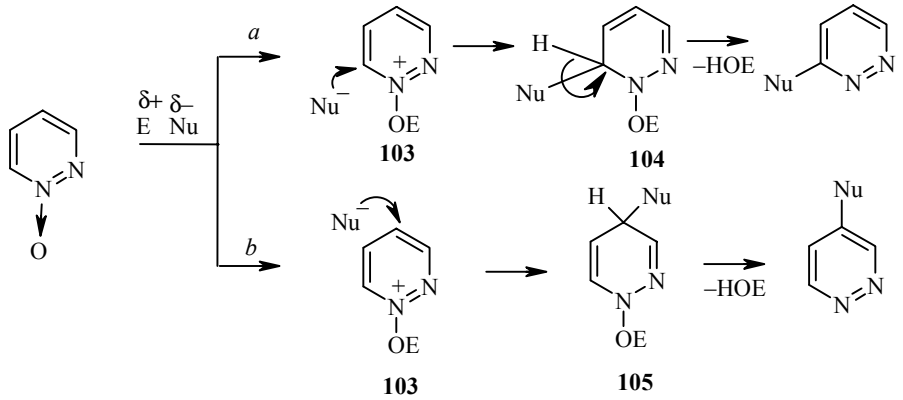
4-Phenylphthalazine 2-oxide **101** reacts with acetophenone in aqueous alkaline solution with the formation of the 1-phenacyl derivative **102** [78].




**101** **102**

### 2.2. Nucleophilic Substitution of Hydrogen with the Participation of the N-Oxide Function

The nucleophilic substitution of hydrogen in pyridazine 1-oxides accompanied by loss of the oxide group is realized according to one of the directions shown below.

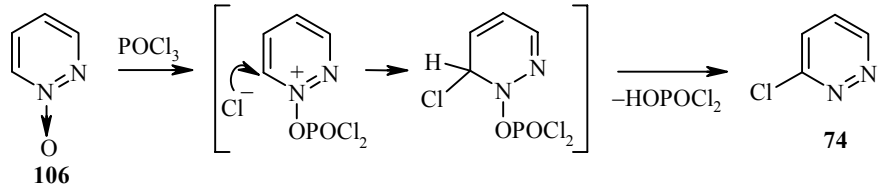



**103** **104** **103** **105**

In both cases reaction takes place through the intermediate cation **103** which then adds nucleophile. The adducts **104** and **105** are aromatized with fission of the HOE particle. The process does not therefore require an external oxidizing agent, the role of which in this particular sense is played by the N-oxide function. Route *a*

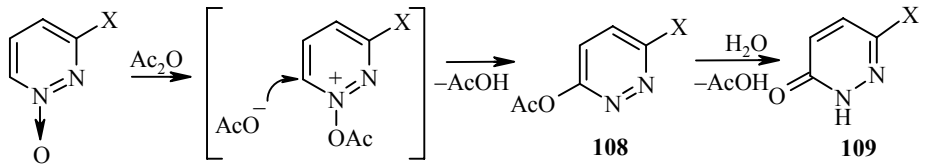
occurs for substrates unsubstituted at the $C_{(6)}$ atom and route *b* when the α position is occupied. Typical conversions of a similar type are the halogenation of N-oxides with phosphorus oxychloride and the Katady rearrangement proceeding under the action of carboxylic acid anhydrides and giving pyridazin-3-ones.

Treatment of pyridazine 1-oxide (**106**) with phosphorus oxychloride leads to 3-chloropyridazine (**74**) [14]. Under the same conditions 3-methoxy- and 3,6-dimethylpyridazine 1-oxides are converted into the 6-chloro and 4-chloro derivatives respectively [14].




**106** **74**

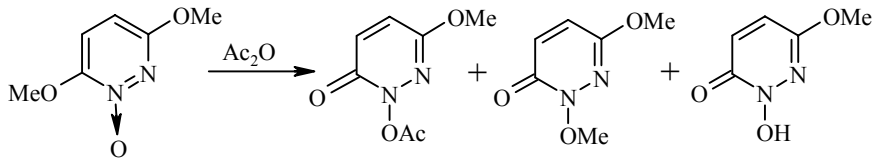
Refluxing the N-oxide **107** in acetic anhydride and then hydrolyzing the initially formed acetoxy derivative **108** transforms it into the pyridazinones **109** [14].



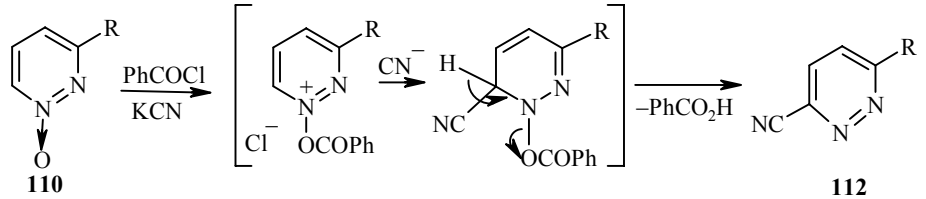

**107** **108** **109**

X = OH, $NH_2$

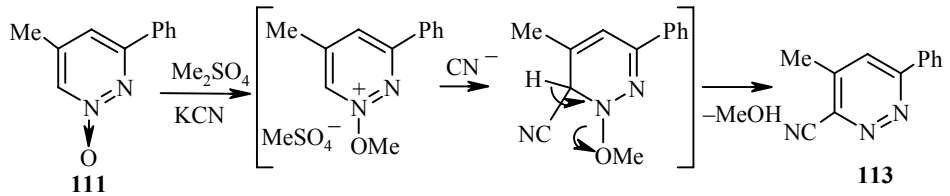
When a methyl or alkoxyl group, or a halogen atom is present in the α-position to the N-oxide function the reaction proceeds ambiguously leading to a complex mixture of products of nucleophilic substitution and hydrolysis [14].



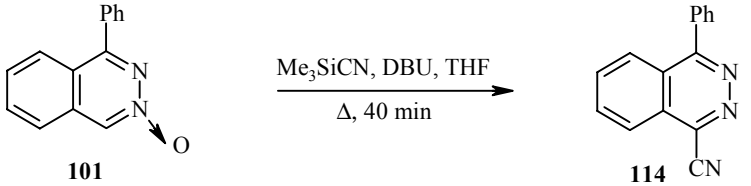

A convenient method of introducing a cyano group into the heterocycle is the reaction of N-oxides with cyanide ion in the presence of acylating or alkylating agents. The interaction of pyridazine oxides **110** and **111** with cyanide ion and benzoyl chloride (or dimethyl sulfate) leads to the formation of 3-cyanopyridazines **112** and **113** [14].



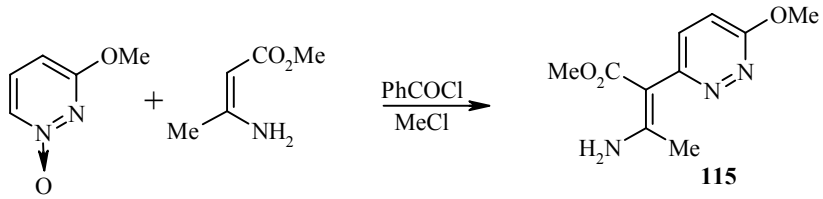

**110** **112**



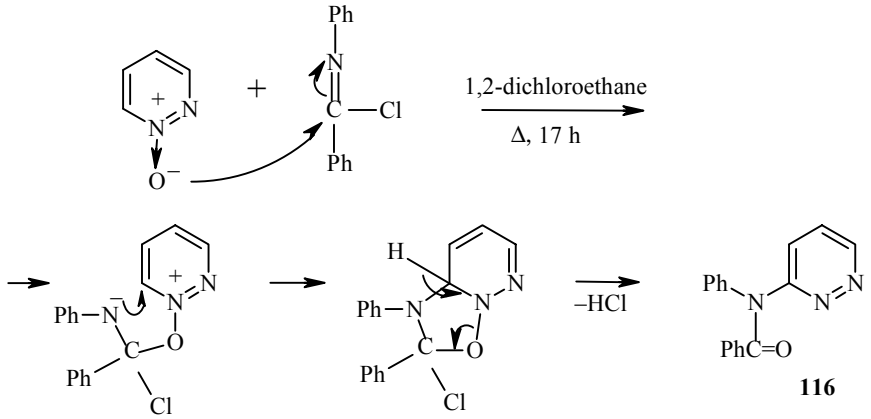
The phthalazine oxide (**101**) is converted on treatment with trimethylsilyl cyanide into nitrile **114** in 76% yield. The reaction proceeds under interphase catalysis conditions [79].



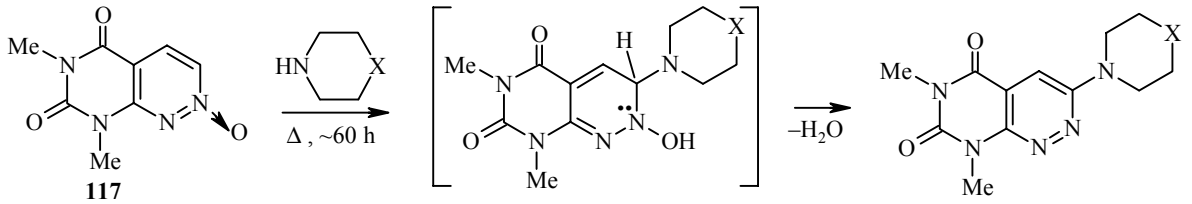
Other substituents may also be introduced analogously into the pyridazine ring. 3-Methoxypyridazine 1-oxide reacts with β-aminocrotonic acid methyl ester in the presence of benzoyl chloride forming α-(6-methoxy-3-pyridazinyl)-β-aminocrotonate (**115**) in 48% yield [80].



On reacting N-phenylbenzimidoyl chloride with pyridazine 1-oxide 3-(N-benzoylanilino)pyridazine (**116**) is obtained in 18% yield. The imidoyl chloride acts as an alkylating agent and a nucleophile simultaneously. The reaction is claimed to proceed according to the following scheme [81].

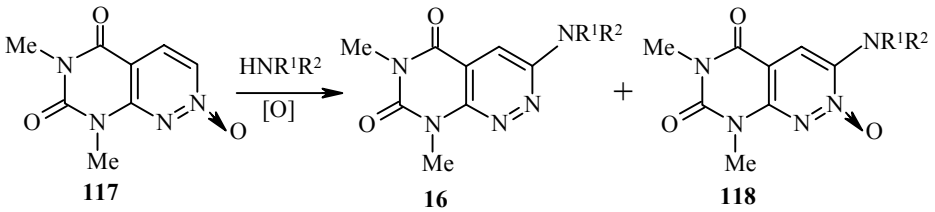


On extended refluxing of 6,8-dimethylpyrimido[4,5-*c*]pyridazin-5,7(6H,8H)-dione (**117**) $N_{(2)}$-oxide in an excess of piperidine or morpholine the 3-piperidino or 3-morpholino derivatives **16** were formed in yields of 42 or 36% respectively [82]. Compound **117** does not react with alkylamines at room temperature.



**117** **16** (X = $CH_2$, O)

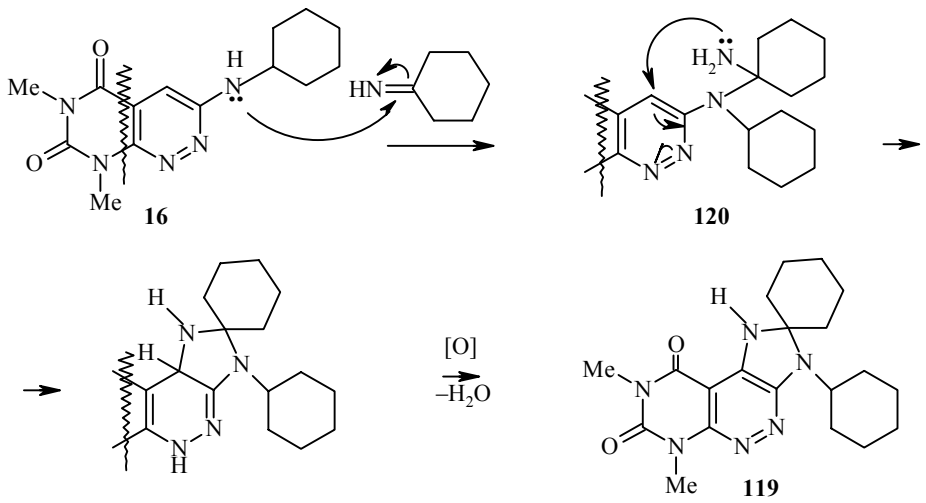
It is known that nucleophilic substitution of a hydrogen atom in azine N-oxides is accelerated on addition of oxidizing agents [6], and in this case retention of the N-oxide function is possible. In reality the interaction of N-oxide **117** with alkylamines in the presence of $KMnO_4$ or $AgPy_2MnO_4$ also proceeds with the formation of a difficultly separable mixture of 3-amino derivatives **16** and **118** (total yield 50-68%), the latter predominates in the majority of cases [82].



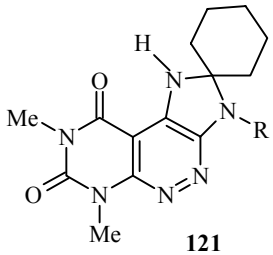
**117** **16** **118**

$R^1$, $R^2$: H, H; H, Me; H, Et; H, Pr; H, $PhCH_2$; Me, Me; H, $C_6H_{11}$; $(CH_2)_5$; $(CH_2)_2O(CH_2)_2$

In the case of cyclohexylamine, imidazoline **119** is formed in 5% yield in addition to the corresponding amines **16** and **118** (A. V. Gulevskaya, A. F. Pozharskii, and D. V. Besedin, unpublished results). Probably in the course of the conversion **117**→**119** the 3-amino derivative **16** [$R^1R^2 = (CH_2)_5$] interacts with cyclohexanone imine formed *in situ* by the oxidation of cyclohexylamine. Subsequent intramolecular nucleophilic attack of the amino group of intermediate **120** at the $C_{(4)}$ atom of the pyridazine ring leads to the spirocyclic product **119**.



**16** **120** **119**



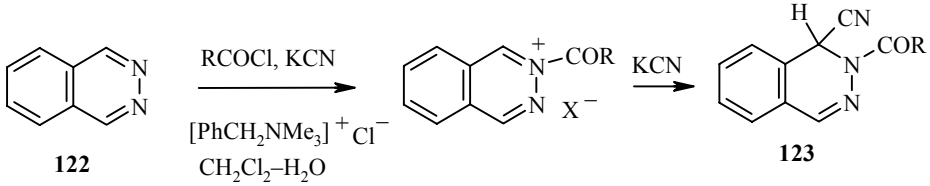
**121** R = Et, Pr

The synthesis of spiranes **119** and **121** by the action of cyclohexylamine on the known amines **16** ($R^1R^2$ = H, Et; H, Pr; $(CH_2)_5$, $NR^1R^2$ = cyclohexylamino) under the same conditions serves as experimental confirmation of the mechanism proposed.

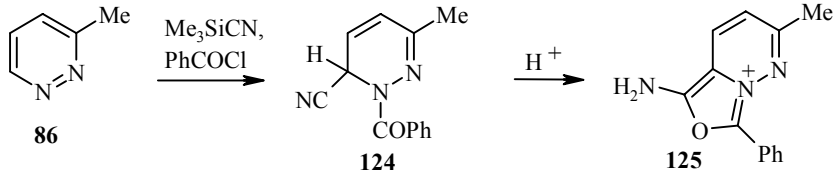
## 3. INTERACTION OF PYRIDAZINIUM CATIONS WITH NUCLEOPHILES

### 3.1. The Reissert Reaction

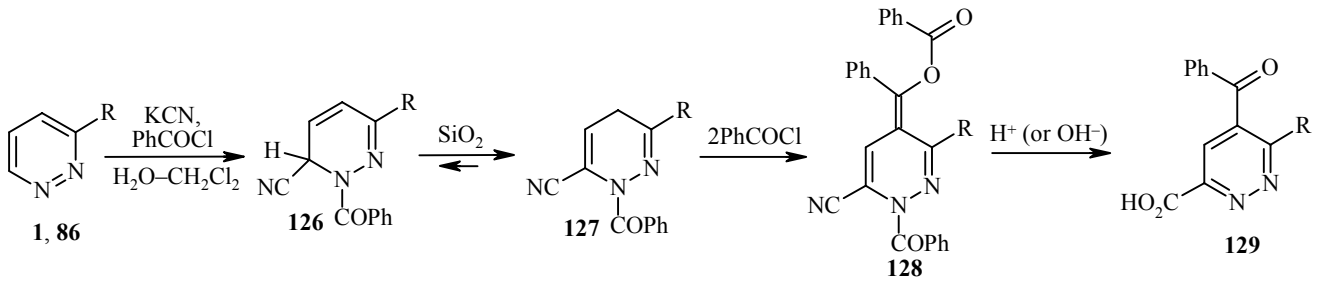
Condensed pyridazines undergo the Reissert reaction under classical conditions with difficulty [83, 84]. However in the presence of a phase transfer catalyst phthalazine **122** interacts smoothly with potassium cyanide and acyl chlorides to form adducts **123** [85, 86].



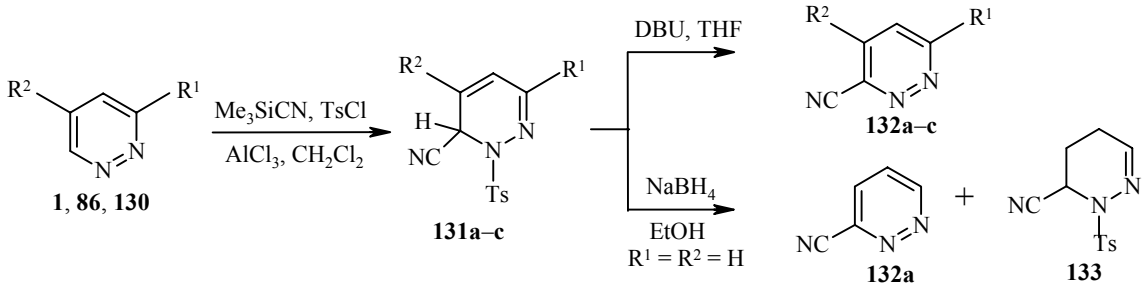

It is interesting that monocyclic pyridazines also participate in this reaction [87-89]. On treatment of 3-methylpyridazine **86** with trimethylsilyl cyanide and freshly distilled benzoyl chloride the Reissert compound **124** is formed (41% yield) [87]. On using undistilled benzoyl chloride containing admixture of water and HCl the product of further cyclization of compound **124** was formed, *viz*. the oxazolopyridazinium salt **125** [87].




The interaction of pyridazines **1** and **86** with KCN and benzoyl chloride in water–$CH_2Cl_2$ system is complicated by the isomerization of the Reissert compound formed initially. The 2,3-dihydro adduct is practically completely tautomerized on silica gel into the 2,5-dihydro derivative **127**. The latter is subject to further double benzoylation with the formation of the enol ester **128**, hydrolysis of which leads to 5-benzoylpyridazine-3-carboxylic acid **129** [88].



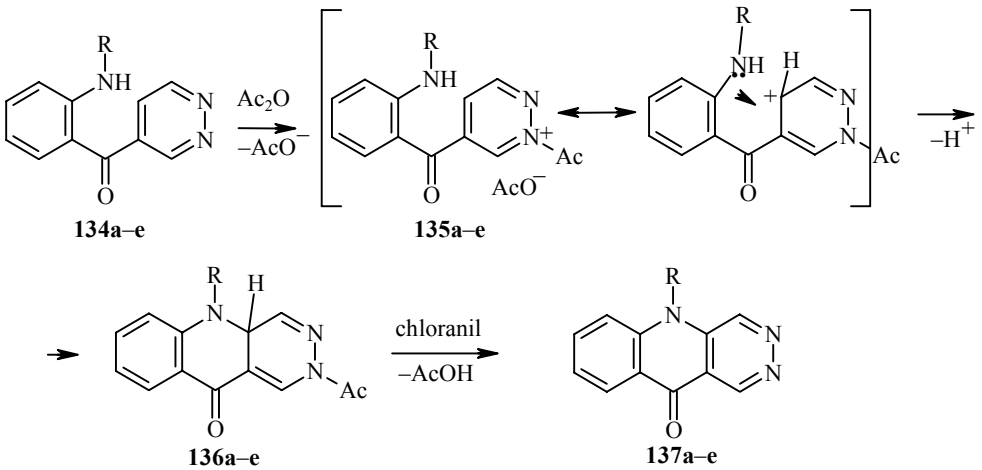

The normal Reissert adducts **131** obtained from compounds **1**, **86**, and **130** are converted under the action of DBU into 3-cyanopyridazines **132a-c** in good yield [88]. The reaction of $NaBH_4$ with compound **131a** forms a mixture of nitrile **132a** (29% yield) and tetrahydropyridazine **133** (29% yield).




**130** $R^1$ = H, $R^2$ = Me; **131, 132 a** $R^1 = R^2$ = H, **b** $R^1$ = Me, $R^2$ = H, **c** $R^1$ = H, $R^2$ = Me

### 3.1. Other Reactions

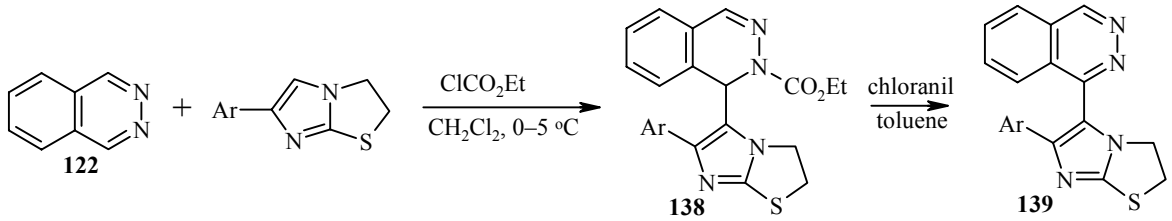
N-Acylpyridazinium salts also react readily with other types of nucleophiles giving products of substitution of hydrogen atoms. The 2-acetyldihydrodiazaacridones **136a-e** are formed in 44-51% yield on heating 4-(*o*-alkylaminobenzoyl)pyridazines **134a-e** in acetic anhydride (evidently through the intermediates **135a-e**). Compounds **136a-e** may then be oxidized with chloranil to compounds **137a-e** (29-37% yields) [90,91].



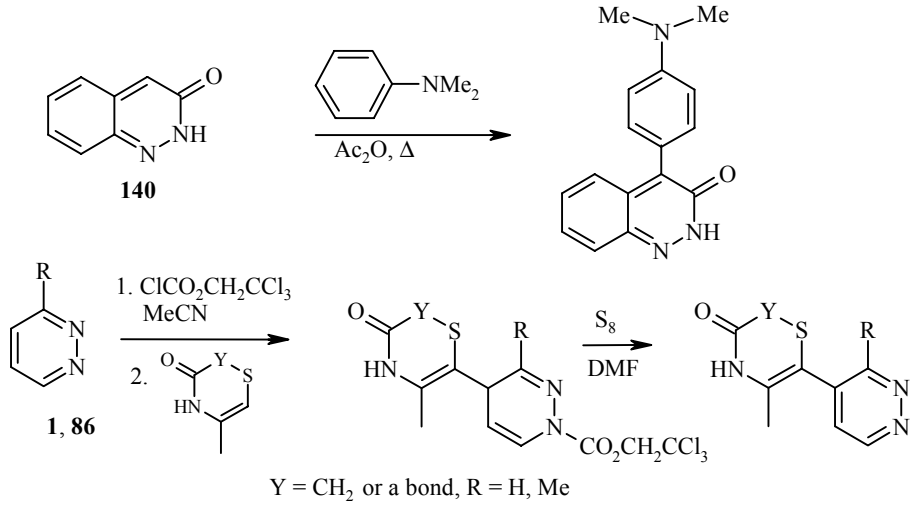

**134–137 a** R = Bu, **b** R = $PhCH_2$, **c** R = $(CH_2)_2OH$, **d** R = $CH_2CH(OMe)_2$, **e** R = $CH_2$–CH=$CH_2$

Diazaacridones **137** may be obtained in 81-88% yield by heating the known prepared salt **135** in 0.1 N NaOH solution in the presence of oxygen of the air.

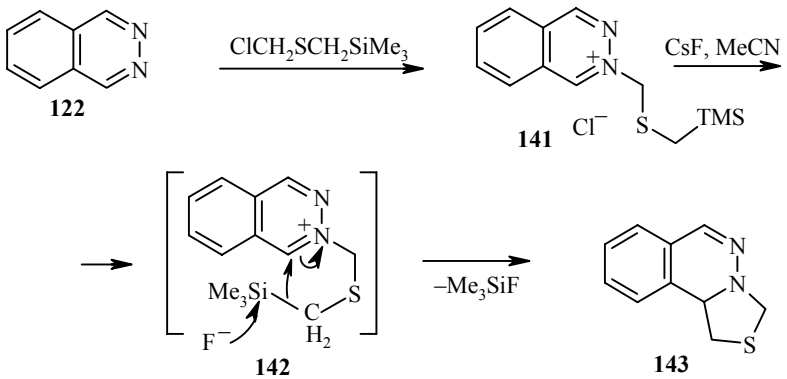
Previous N-acylation enables substitution of the hydrogen atom by residues of neutral C-nucleophiles to be effected under mild conditions. For example, phthalazine **122** adds 6-aryl-2,3-dihydroimidazolo[2,1-*b*]-thiazole in the presence of ethyl chloroformate. The adduct **138** (62% yield) may be oxidized by chloranil to compound **139** (32% yield) [92].



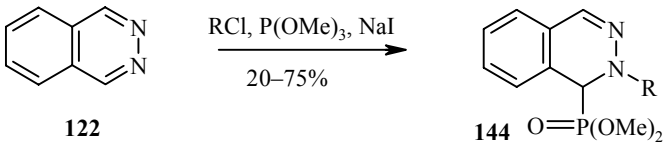

A similar approach enables the C-arylation of cinnolone (**140**) [93], pyridazine (**1**), and 3-methylpyridazine (**86**) [94,95].




Quaternization of phthalazine (**122**) with chloromethyl trimethylsilylmethyl sulfide with subsequent treatment of the quaternary salt **141** obtained in 96% yield with cesium fluoride leads to the formation of thiazolino[4,3-*a*]phthalazine (**143**) in 92% yield [96].

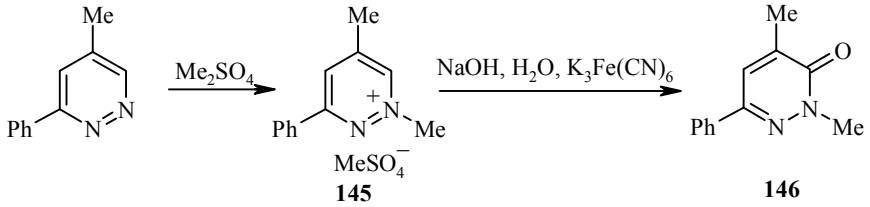


A rare example of the introduction of a P-nucleophile into the pyridazine ring was described in [97]. Phthalazine (**122**) reacts with trimethyl phosphite and acyl chlorides in the presence of sodium iodide forming, as a result of sequentially occurring Reissert and Arbuzov reactions, the dimethyl phosphoryl adducts **144**.

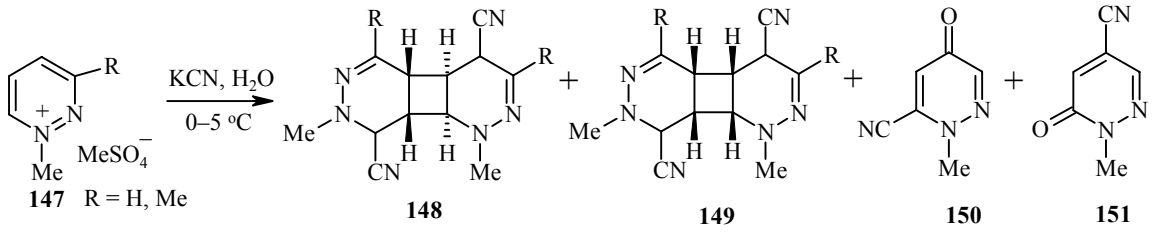



R = $MeSO_2$, $PhSO_2$, MeCO, PhCO, $Ph_2NCO$

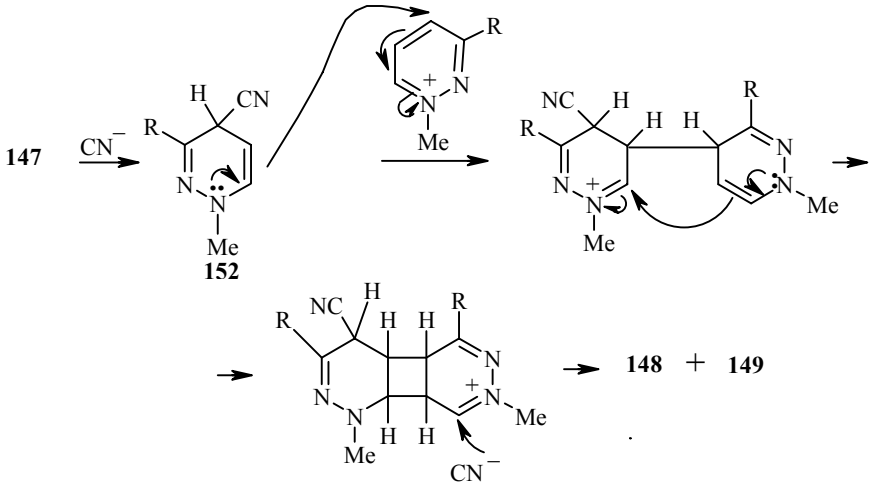
The pyridazinium salts **145** enter into the Dekker reaction, however the product of oxidative hydroxylation, the pyridazinone **146**, is obtained in only 22% yield [98].



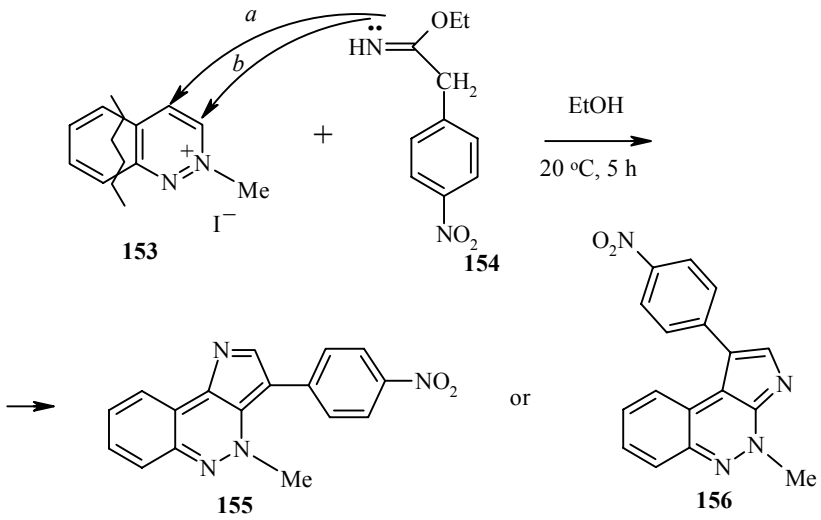

The 1-methylpyridazinium salts **147** are cyclodimerized in aqueous solution in the presence of cyanide ion. In addition to dimers **148** (10-20% yield) and **149** (2-5% yield) the pyridazinones **150** and **151** were isolated in less than 2% yield [99, 100].



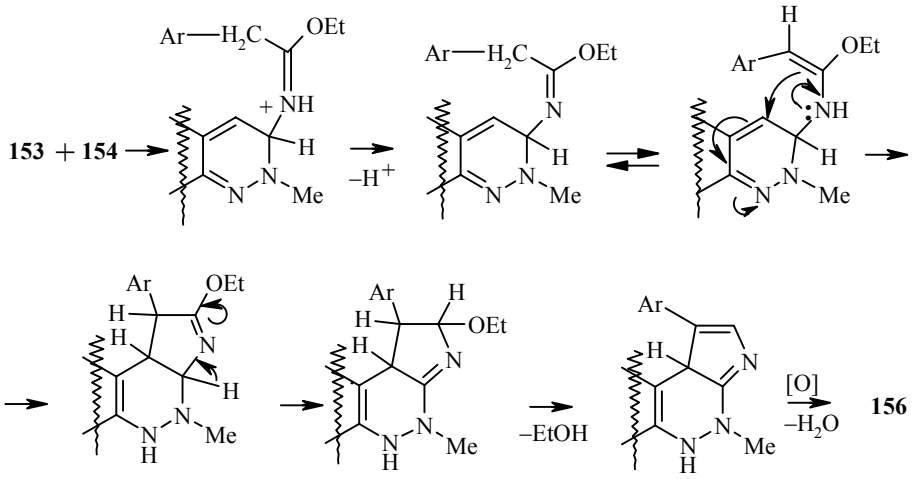

The mechanism of formation of dimers **148** and **149** presumably includes nucleophilic attack of the Reissert adduct **152** on the initial cation and subsequent intramolecular cyclization as shown in the scheme.



On treating 2-methylcinnolinium iodide (**153**) with iminoether **154** a pyrrolocinnoline is formed in 68% yield [101], for which the authors did not decide on which of the two possible structures (**155** or **156**). In our opinion structure **156** is more probable since position 3 in the 2-methylcinnolinium ion is more electron-deficient and consequently the imine nitrogen atom will probably attack it in the first step.




The mechanism of this interesting reaction in which iminoether **154** acts as a bifunctional nucleophile may be represented by the scheme below. Oxygen of the air most likely plays the role of oxidizing agent, although it is impossible to exclude that the iminoether (due to the nitro group), which is taken in excess, is the dehydrogenating agent.




1-Methyl-3,6-bis(dimethylamino)pyridazinium iodide adds Grignard reagent at the $C_{(4)}$ atom [102].

## CONCLUSION

The data considered in the present review indicate that practically all types of $S_NH$ reaction occurring in other azine series are natural to pyridazine. At the same time certain pyridazine systems, especially condensed systems, have an increased inclination towards multiple nucleophilic substitution of hydrogen. Among these,

tandem $S_NH$–$S_NH$ reactions stand out in preparative and theoretical significance. These proceed under the action of bifunctional nucleophiles and enable annelation of other heterocycles to a pyridazine ring in one process. The investigation of these conversions will in the future become extremely promising and interesting, equal to the search for other heterocyclic substrates capable of displaying similar reactivity.

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