TRANSFORMATIONS OF NITROPYRIMIDINES BY ACTION OF C-NUCLEOPHILES

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Abstract - The addition of C-nucleophiles to 5-nitropyrimidines, to some of their [1,5-*a*]pyrazolo- or triazolo-annelated systems, and their subsequent ring transformations have been reviewed. The ring transformations involving the replacement of the $N_{(3)}$-$C_{(4)}$-$C_{(5)}$ fragment of the pyrimidine ring, the $N_{(1)}$-$C_{(5)}$-$C_{(6)}$, the $N_{(1)}$-$C_{(2)}$-$N_{(3)}$ or the $N_{(1)}$-$C_{(2)}$ fragment by structural parts of different C-nucleophilic agents are summarized; possible pathways, involving these transformations are discussed.

INTRODUCTION

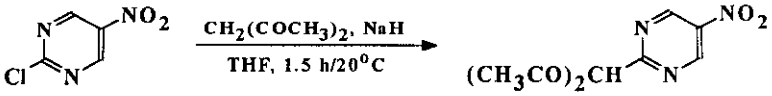
Introduction of the nitro group into six-membered azaheterocycles considerably increases the π-deficiency of these systems.[1] Due to the electronic effects of both aza and nitro groups nitroazines usually easily react with nucleophiles although sometimes quaternisation of the ring nitrogen is necessary to enhance further the reactivity of the system.

This review covers reactions of 5-nitropyrimidines with C-nucleophiles and deals with addition, substitution, and ring transformation.

1. ADDITION AND SUBSTITUTION REACTIONS

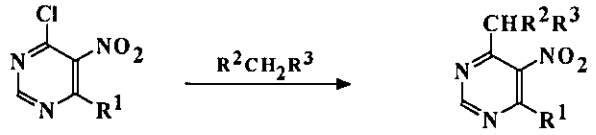
Interaction of 2- or 4-chloro-5-nitropyrimidines with CH-active dicarbonyl compounds, such as malonic esters, acetoacetic esters or cyanoacetic esters in basic medium leads to substitution of the halogen atom, yielding the 5-nitropyrimidines (**1**) and (**2**) (Scheme 1).[2, 3]

Scheme 1



1

Yield 6%

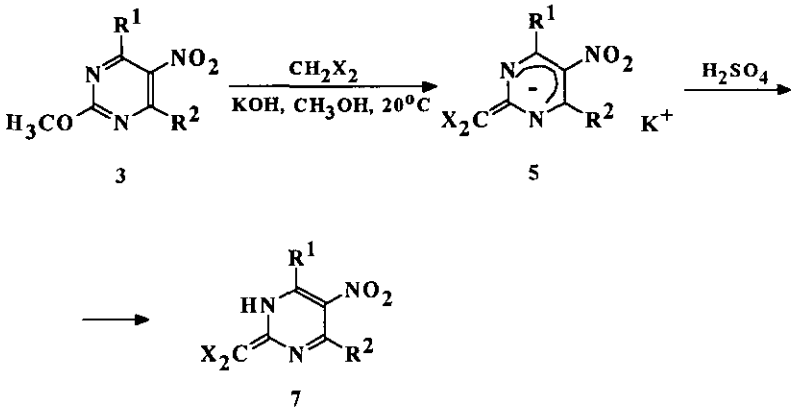


2

R^1	R^2	R^3	Conditions	Yield, %
OMe	Ac	Ac	NaH, DMF, 1 h/20°C	43
NHMe	COOEt	COOEt	NaOH, acetone, 50 min/0°C	72
NHMe	Ac	COOEt	NaOH, acetone, 50 min/0°C	66
NHMe	CN	COOEt	NaOH, acetone, 50 min/0°C	79
$NHCH_2C{=}C(Me)CH_2OC(Me)_3$	Ac	COOEt	NaOH, acetone, 50 min/0°C	85

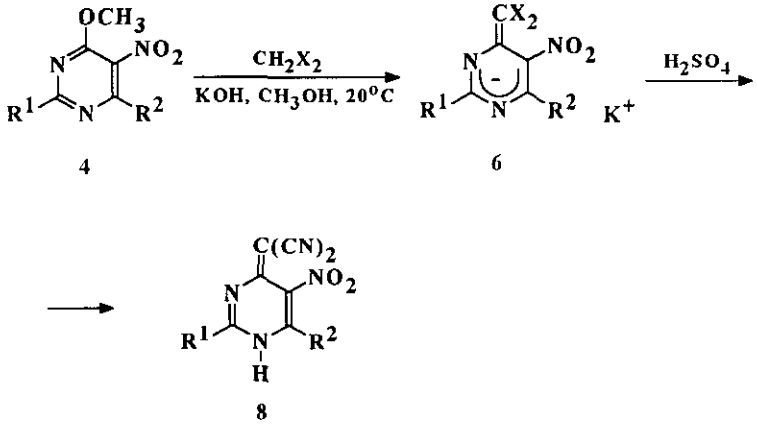
The reactions of the 2- or 4-methoxy-5-nitropyrimidines (**3**) and (**4**) with malononitrile carbanion result in formation of 2- or 4-dicyanomethylene-5-nitropyrimidinides anions (**5**) and (**6**), their potassium salts being obtained as deeply coloured crystals (Scheme 2).[2, 4] With acetylacetone hardly any reaction occurs.

Scheme 2



3 5 7

R^1	R^2	X	Reaction time, h	Yield, %
H	H	Ac	5	3
H	H	CN	1	55
OMe	H	CN	1	71
OMe	OMe	CN	3.5	77

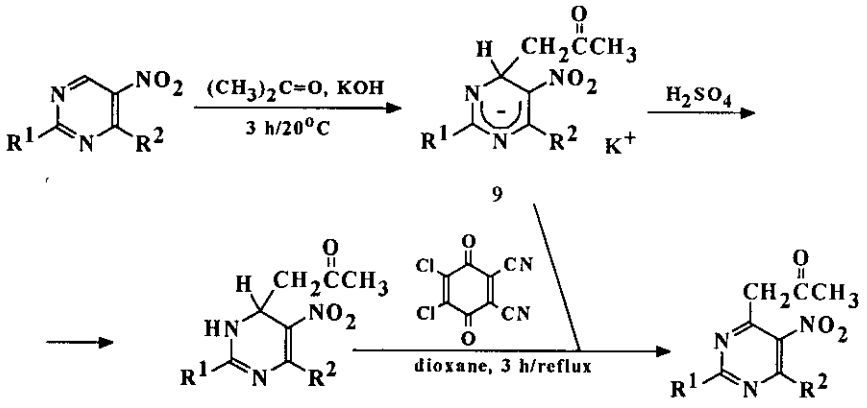


4 6 8

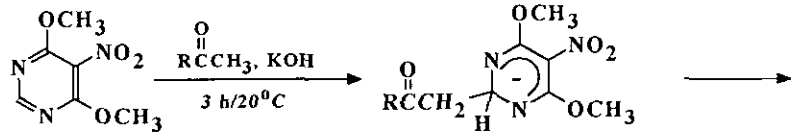
R^1	R^2	X	Reaction time, h	Yield, %
H	H	CN	1.5	35
H	OMe	CN	5	76
OMe	H	CN	1	71
OMe	OMe	CN	1	77
H	OMe	Ac	3 5	0

Not in one of above mentioned cases the formation of intermediary anionic Meisenheimer-type σ-adducts was observed nor by nmr and/or uv spectroscopy. Moreover, no substitution reaction of the nitrogroup has been found. Treatment of the salts (**5**) and (**6**) with sulfuric acid affords the stable dihydropyrimidines (**7**) and (**8**). Acetone (pK_a 20.0), a more weaker CH-acid than malononitrile (pK_a 11.2) and acetylacetone (pK_a 8.9), reacts with methoxy-5-nitropyrimidines in a different way,[4, 5] in stead of replacement of the methoxy group the nucleophilic attack takes place at the unsubstituted carbon of the pyrimidine ring (Scheme 3).[6, 7] Thus, on heating of 2-methoxy-, 4-methoxy- or 2,4-dimethoxy-5-nitropyrimidines with acetone in presence of potassium hydroxide the potassium salts of 4-acetonyl-3,4-dihydro-5-nitropyrimidinides (**9**) and (**10**) were obtained, being isolated as deep red crystals. When both 2 and 4 positions in the pyrimidine ring are unsubstituted the $C_{(4)}$ position is the most preferential site for nucleophilic attack. When treated with diluted sulfuric acid (**9**) is protonated yielding the 3,4-dihydropyrimidines (**11**). Oxidation of **9** and **10** as well as **11** leads to the acetonyl-5-nitropyrimidines (**12**) and (**13**) respectively.

Scheme 3



R^1	R^2	Yield **9**, %
OMe	OMe	79
OMe	H	68
H	OMe	20
H	H	25



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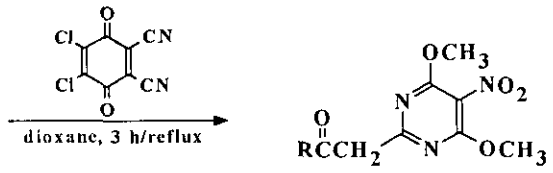
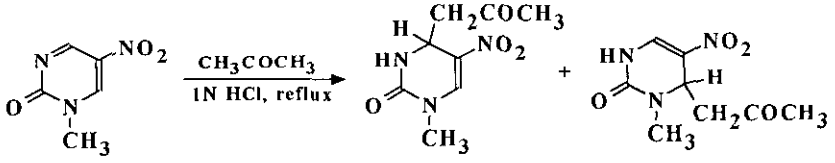


13

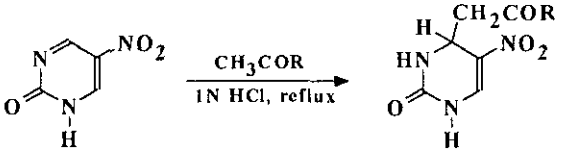
R	Yield **10**, %
Me	86
Ph	62

Quite stable adducts could be isolated when the 1,2-dihydro-5-nitropyrimidin-2-ones (**14**) and (**15**) were treated with ketones or ketoesters in acidic media (Scheme 4) [8] In the reaction of (**14**) with acetone two isomeric σ-adducts were obtained

Scheme 4



14

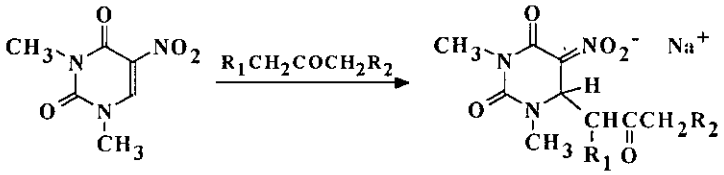


15

R	Reaction time, h	Yield, %
H	5	82
Me	2	76
COOEt	5	61

Use of base catalysts is required to get 1,3-dimethyl-5-nitrouracil (**16**) reacting with CH-active carbonyl compounds (Scheme 5).[9] Deeply coloured sodium salts were obtained

Scheme 5



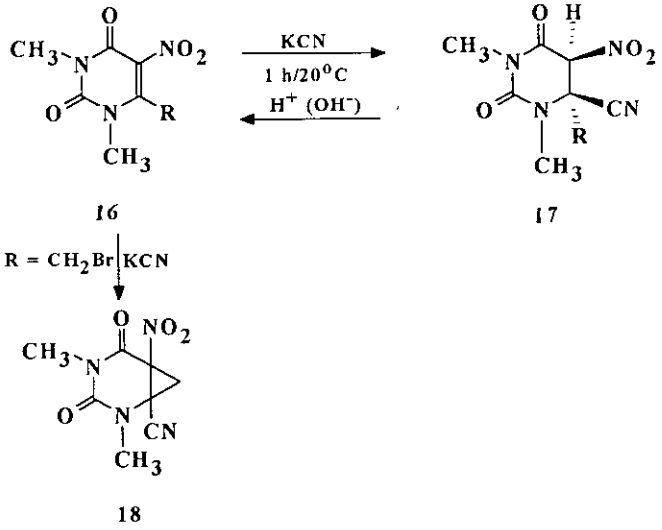
16

R^1	R^2	Conditions	Yield, %
H	H	MeONa, MeOH, 2 h/reflux	73
Me	H	MeONa, MeOH, 2 h/reflux	31
H	Me	MeONa, MeOH, 2 h/reflux	25
H	COOEt	EtONa, EtOH, 20 h/reflux	58
COOEt	COOEt	EtONa, EtOH, 20 h/reflux	28

The bifunctional cyanide ion has been found to react with 5-nitrouracil derivatives as a carbon-centered reagent [10, 11] Treatment of these compounds with potassium cyanide leads to the formation of adducts (**17**) This reaction proved to be stereospecific The nitro group and the substituent R are preferentially situated at the *trans*-equatorial positions (Scheme 6) It is of interest to mention that 6-bromomethyl-5-nitrouracil (**16**) (R= CH_2Br) when reacting with potassium cyanide affords 1-cyano-2,4-dimethyl-6-nitro-2,4-diazabicyclo-[4 1 0]heptane-3,5-dione (**18**), convincingly showing that the initially formed adduct has indeed structure (**17**) (R = CH_2Br) formed, in which an intramolecular cyclization takes place

The chemical behaviour of nitropyrimidines being annelated to azoles considerably differs from that of the monocyclic analogs. The aromaticity indices estimated according to the method, which takes into account changes of the bond order values,[1, 12] show that the aromaticity of the pyrimidine ring in 6-nitropyrazolo- or 6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidines corresponds to about 60% of that of benzene

Scheme 6

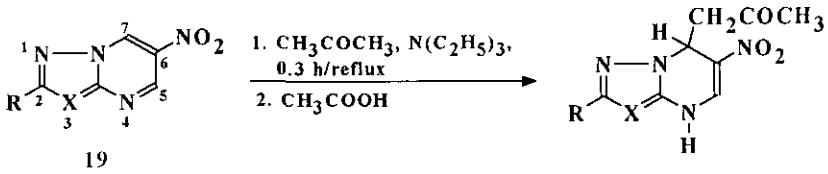


16 17 18

R	Yield, %
Me	95
Et	63
CH=CHPh	92

So, it appears that condensed nitroazines more easily react with a greater range of nucleophiles (ketones, aromatics such as pyrroles, indoles, polyphenols and amines) than their monocyclic analogs, rather stable adducts are formed, as for instance, when heating 6-nitroazolo[1,5-*a*]pyrimidines (**19**) with acetone in the presence of triethylamine (Scheme 7) [13]

Scheme 7

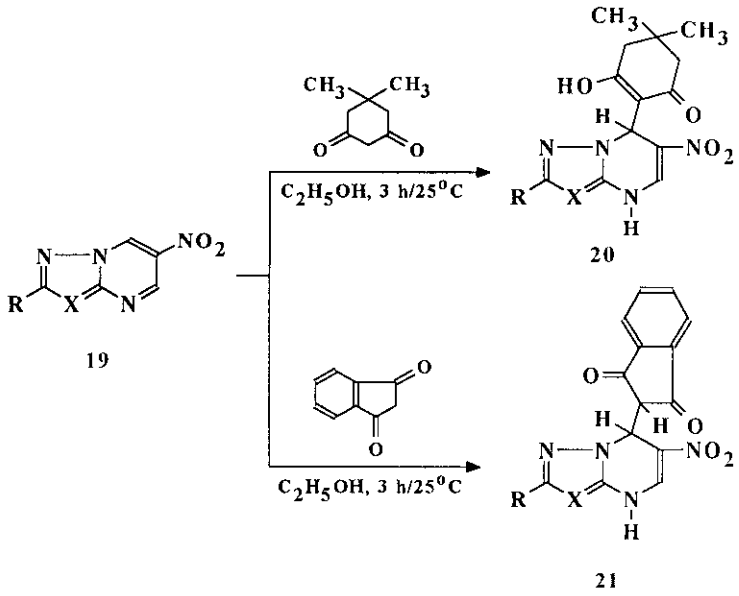


19

R	X	Yield, %	R	X	Yield, %
H	N	84	COOEt	N	76
Me	N	82	Ph	N	73
SMe	N	80	NH_2	N	26
CF_3	N	71	NMe_2	N	28
Cl	N	74	H	CCOOEt	83

Also with cyclic β-diketones, such as dimedone or indandione (Scheme 8) [14] without any additional activation of reagents and/or substrate the azolopyrimidines (**19**) give stable adducts It is of interest to mention that the dimedone derivatives (**20**) are present in solutions as well as in crystals in the keto-enol form, whereas according to X-ray data indandione derivatives (**21**) exist in the diketonic form.

Scheme 8

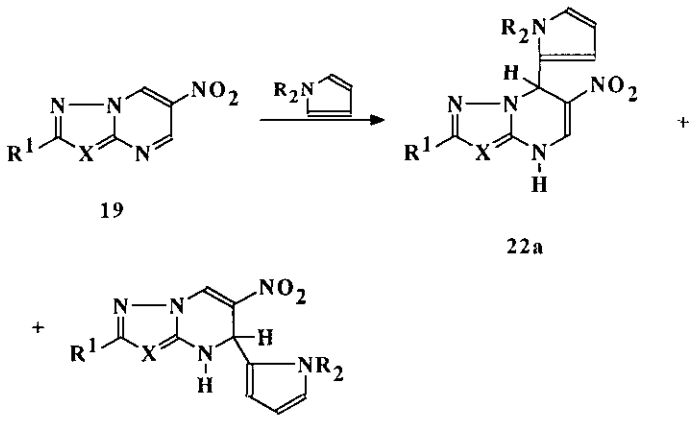


R	X	Yield, %	
		20	**21**
H	N	64	47
Me	N	68	51
Et	N	85	57
SMe	N	88	-
CF_3	N	43	-
H	CCOOEt	51	45

C-C Bond formation between the pyrimidine ring in **19** and azoles such as pyrrole and indole has also been found, the latter reacting as nucleophile Heating of the compounds (**19**) with pyrrole or *N*-methylpyrrole in dimethylsulfoxide or in ethanol leads to the formation of $C_{(7)}$ and $C_{(5)}$ adducts (**22a,b**) in high yields (Scheme 9).[15] In dioxane the yields of the compounds (**22a,b**) (R^1 = R^2 = Me) were low; only 23 and 11%

respectively Ratio of the isomeric adducts depends on the nature of the solvent used Whereas in dimethylsulfoxide the ratio **22a/22b** varies between 1.5 and 2.2, in ethanol this ratio lies between 3 and 8 The high yields of **22a** which are obtained in ethanol allows isolation of this isomer by means of triple recrystallization of the reaction products from ethanol.

Scheme 9

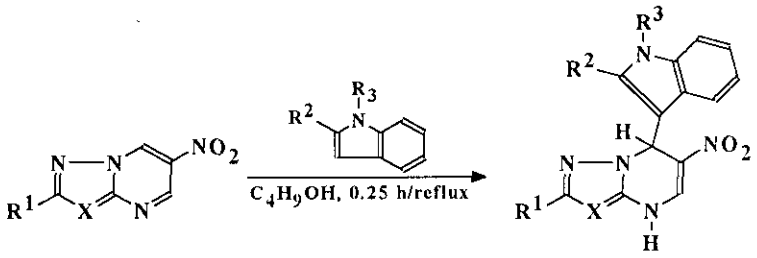


19 **22a** **22b**

R^1	X	R^2	Yield, % DMSO, 15 min/100°C		EtOH, 2 h/reflux	
			22a	**22b**	**22a**	**22b**
H	N	H	50	35	73	23
Me	N	H	56	24	78	18
SMe	N	H	49	26	76	14
H	CCOOEt	H	58	27	70	22
Ph	CH	H	48	21	75	15
H	N	Me	47	28	82	10
Me	N	Me	53	37	84	12
COOEt	N	Me	65	22	80	18

Reaction of the nitroazolopyrimidines (**19**) with indoles only yields the $C_{(7)}$-dihydro adducts (**23**) (Scheme 10) [16-18] No indication for the formation of $C_{(5)}$-adducts was found

Scheme 10



19 23

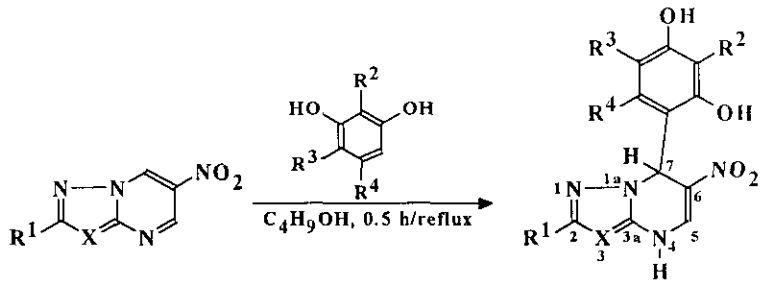
R^1	X	R^2	R^3	Yield, %	R^1	X	R^2	R^3	Yield, %
H	N	H	H	84	COOEt	N	Me	H	77
Me	N	H	H	90	Ph	N	H	Me	78
COOEt	N	H	H	75	H	CCOOEt	Me	H	82
H	CCOOEt	H	H	85	H	CNO_2	Me	H	76
H	CNO_2	H	H	74	H	CCN	Me	H	80
H	CCN	H	H	64	H	CCOOEt	H	Me	88
H	N	Me	H	95	H	CNO_2	H	Me	80
Me	N	Me	H	82					

Similarly, 6-nitroazolo[1,5-*a*]pyrimidines (**19**) (X = CNO_2, CCOOEt, CCN) react with a range of polyphenols leading to $C_{(7)}$-adducts (**24**) (Scheme 11).[18-21] The presence of electron-withdrawing substituents, such as bromine or acetyl group, in the polyphenol does not prevent the addition, however 2,4-dihydroxybenzoic acid and gallic acid turn out to be inadequate compounds for addition

Heating of the 6-nitrotriazolopyrimidines (**19**) (X = N) with dialkylanilines in butanol leads to the formation of $C_{(7)}$-adducts (**25**) (Scheme 12) [22]

The reactivity of 6-nitroazolopyrimidines towards the nucleophilic reagents mentioned above depends as can be expected, on the π-deficiency of these systems This can be illustrated by the fact that whereas 6-nitropyrazolo[1,5-*a*]pyrimidine does not react with nucleophiles, the presence of electron-withdrawing substituents in the pyrazole ring (**19**), (X = CCOOEt, CNO_2, CCN) facilitates nucleophilic addition Compounds, having an additional nitrogen atom in the azole moiety, *i.e.* 6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidines, also show a greater reactivity. Deactivation of the system occurs on introduction of an amino or dimethylamino group into the azole ring

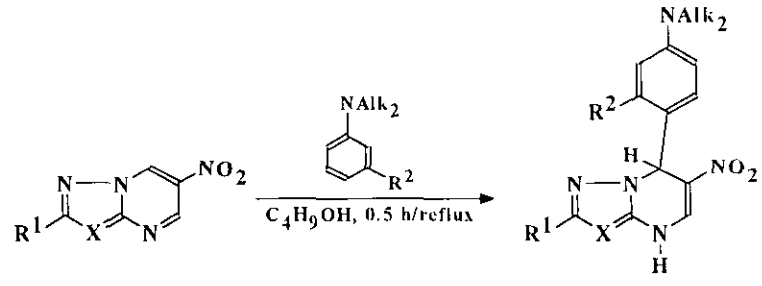
Scheme 11



19 24

R^1	X	R^2	R^3	R^4	Yield, %	R^1	X	R^2	R^3	R^4	Yield, %
H	N	H	H	H	60	COOEt	N	H	H	H	57
H	N	OH	H	H	77	COOEt	N	OH	H	H	94
H	N	H	C_6H_{13}	H	70	CF_3	N	H	H	H	50
H	N	H	H	OH	55	H	CCOOEt	H	H	H	43
H	N	H	Br	H	47	H	CCOOEt	H	Ac	H	39
Me	N	H	H	H	46	H	CCOOEt	H	H	H	41
Et	N	H	H	H	61						

Scheme 12



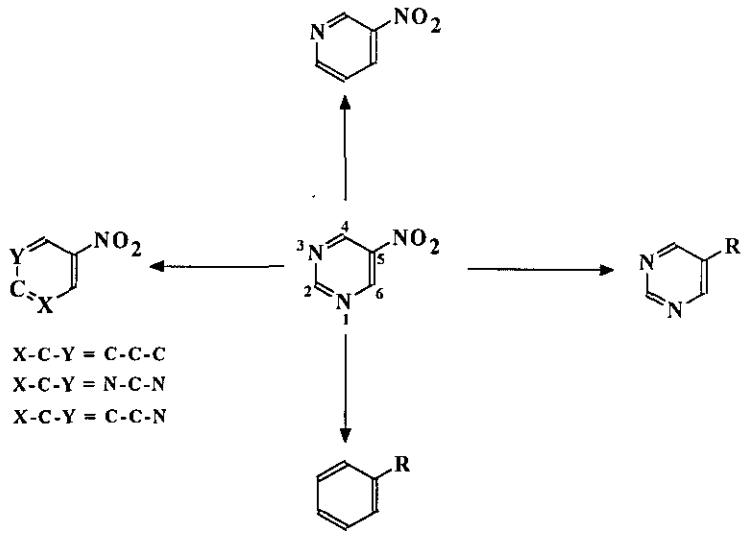
19 25

R^1	X	Alk	R^2	X	Yield, %
H	N	Et	H	N	40
H	N	Et	OH	N	62
Me	N	Et	OH	N	51
CF_3	N	Me	H	N	50
CF_3	N	Et	H	N	32
COOEt	N	Et	OH	N	78

2. RING TRANSFORMATIONS OF NITROPYRIMIDINES BY ACTION OF C-NUCLEOPHILES

Transformations of heterocycles into derivatives of other heterocyclic or carbocyclic systems by a reaction with a nucleophile, involving an addition ring-opening-ring-closure sequence quite often occur in reactions of azines. The pyrimidine ring system is appropriate for such ring transformations. Activation of the pyrimidine ring by either quaternisation or introduction of electron-withdrawing substituents appears to be very often useful for promoting such ring transformations In this respect 5-nitropyrimidine and its derivatives are of particular interest. Extensive investigations have shown that different structural combinations of the 5-nitropyrimidine ring atoms are replacable by different combinations of atoms of C-nucleophile reagents (Scheme 13), *e g* the replacement of the $N_{(3)}$-$C_{(4)}$-$C_{(5)}$ fragment of the pyrimidine ring by the N-C-C atoms of malonamide,[23,24] substitution of the $C_{(5)}$-$C_{(6)}$-$N_{(1)}$ fragment by the C-C-C moiety of dibenzylketone,[27] substitution of the $N_{(1)}$-$C_{(2)}$-$N_{(3)}$ fragment of 5-nitropyrimidine by the C-C-C moiety of acetone or its derivatives,[25-28] as well as by the N-C-N and C-C-N atoms of amidine derivatives,[24, 28-31] the replacement of $N_{(1)}$-$C_{(2)}$ fragment by two carbons atoms of compounds as acetonitrile, acetales or enamines In the following sections these ring transformations will be discussed in more detail

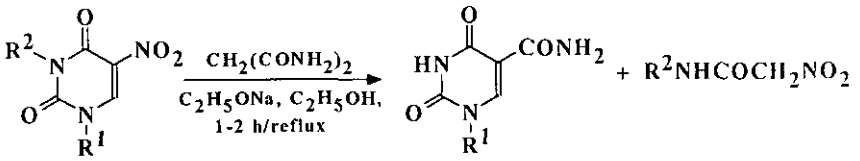
Scheme 13



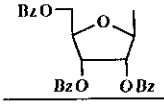
2a. $N_{(3)}$-$C_{(4)}$-$C_{(5)}$ replacement

Substitution of the $N_{(3)}$-$C_{(4)}$-$C_{(5)}$ fragment of the pyrimidine ring by an N-C-C fragment were observed in the reaction of 1,3-dialkyl-5-nitrouracils (**26**) with malonamide in the presence of sodium ethoxide[23, 24] giving rise to the formation of 5-carbamoyluracils (**27**) and nitroacetic acid amides (**28**) in 60-90% yields (Scheme 14).

Scheme 14



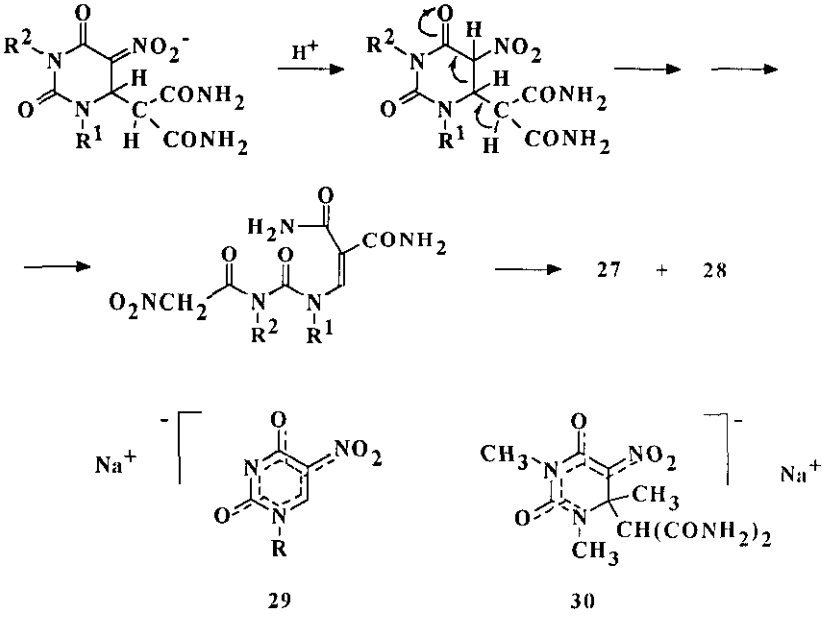
26 **27** **28**

R^1	R^2	Yield, %
Me	Me	63-89
cyclo-C_6H_{11}	Me	89
Me	cyclo-C_6H_{11}	86
	Me	64

5-Nitrouracil and 1-methyl-5-nitrouracil do not undergo this ring transformation probably due to the fact that under the alkaline conditions dissociation of the NH-hydrogen takes place, which leads to the formation of salts (**29**), deactivating the uracil ring for a nucleophilic attack. Also 1,3,6-trimethyl-5-nitrouracil, in which position 6 is blocked for a nucleophilic attack does not undergo the ring conversion, only the product of the Michael addition i e (**30**) could be isolated [23] All these facts suggest the following steps in the ring transformation i) an initial C-addition of the malonamide carbanion at $C_{(6)}$ of 5-nitrouracil (**26**), giving rise to an adduct, ii) ring opening by proton abstraction from the exocyclic β-carbon atom and cleavage of the $C_{(5)}$-$C_{(6)}$ bond; iii) the formation of carbamoyluracil (**27**) from the open-chain intermediate (Scheme 15) These three steps, Addition Nucleophile, Ring Opening and Ring Closure are combined in the anagram "ANRORC mechanism" These three steps in the mechanism are extensively reviewed [32]

Amides of CH-active compounds, such as cyanoacetamide, phenylacetamide or acetoacetamide, do not react with 5-nitrouracils. This fact is quite surprising since these reagents easily cause ring transformation with uracil derivatives which do not contain the nitro group.[33] The suggestion can be made that interaction of these reagents with the C=O or/and C-NO_2 group deactivates the system.

Scheme 15

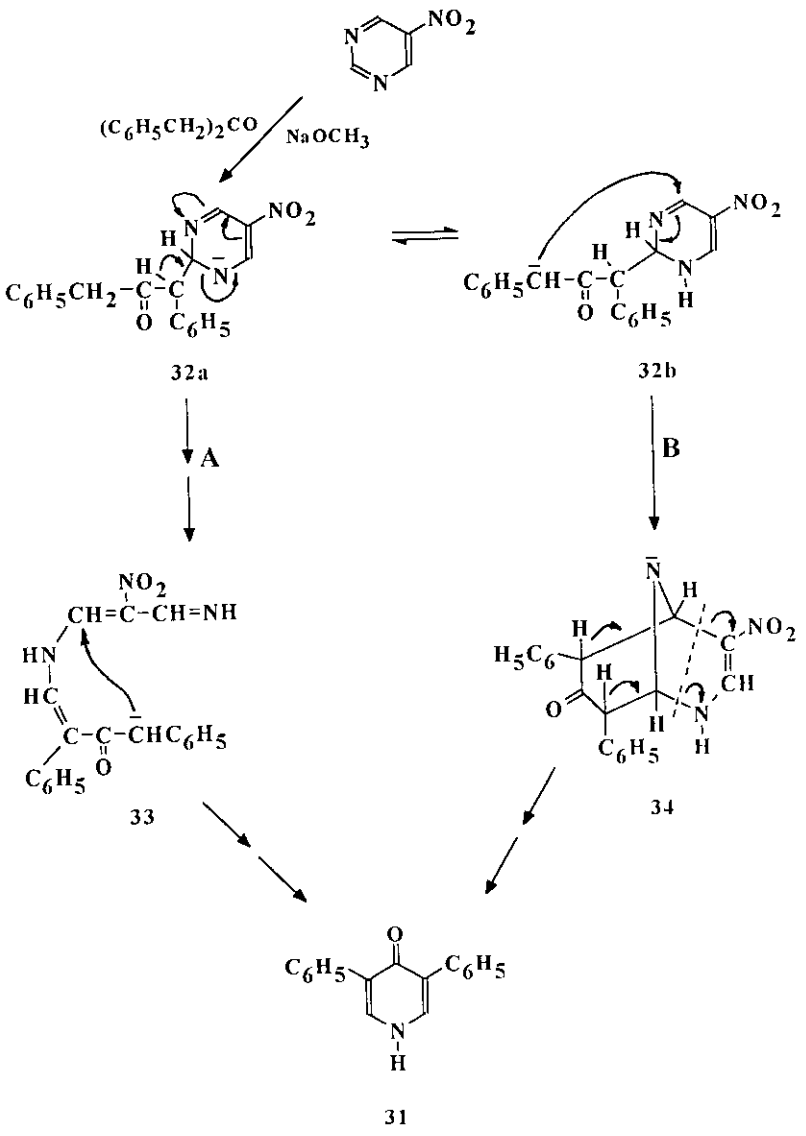


2b. $C_{(5)}$-$C_{(6)}$-$N_{(1)}$ replacement

Substitution of the $C_{(5)}$-$C_{(6)}$-$N_{(1)}$ fragment of the pyrimidine ring by a C-C-C fragment was observed when 5-nitropyrimidine was heated in dimethylsulfoxide for 15 hours with an excess of dibenzylketone in the presence of sodium methoxide, 3,5-diphenyl-4-pyridone (**31**) being obtained in a 43% yield (Scheme 16) [25]

Two plausible mechanisms for this ring transformation can be put forward. Pathway A describes the ANRORC-mechanism involving the initial formation of the anionic σ-adduct (**32a** ⇌ **32b**) as a result of the nucleophilic attack at $C_{(2)}$ of the pyrimidine ring, followed by ring opening into intermediate (**33**) and ring closure of **33** into pyridone (**31**) Pathway B includes the formation of a bicyclic adduct i e **34** . The intermediacy of bicyclic adducts in reactions of π-deficient nitro aromatics with ketones is amply evidenced (see also Scheme 19).

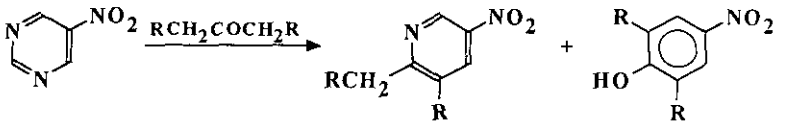
Scheme 16



2c. $N_{(1)}$-$C_{(2)}$-$N_{(3)}$ and $N_{(1)}$-$C_{(2)}$ replacement

It has been observed that interaction of 5-nitropyrimidine with ketones (acetone, diethyl ketone or dibenzyl ketone, acetylacetone, acetoacetic ester) in the presence of triethylamine or potassium hydroxide [2, 25-27] in general proceeds with the formation of 3-nitropyridines (**35**) and/or 4-nitrophenols (**36**) Outcome of the reaction depends on the nature of ketones used (Scheme 17)

Scheme 17



35 36

R	Conditions	Product (Yield, %)
H	Et_3N, EtOH, 24 h/85-90°C	**35** (33)
	KOH, EtOH, 20 h/50°C	**36** (10)
Me	Et_3N, EtOH, 24 h/85-90°C	**35** (30)
	KOH, EtOH, 20 h/50°C	**36** (48)
Ph	Et_3N, EtOH, 24 h/85-90°C	**35** (40)
	Et_3N, EtOH, 24 h/120-130°C	**35** (10) + **36** (11) + **31** (28)
	KOH, EtOH, 3 h/ambient	**36** (65)

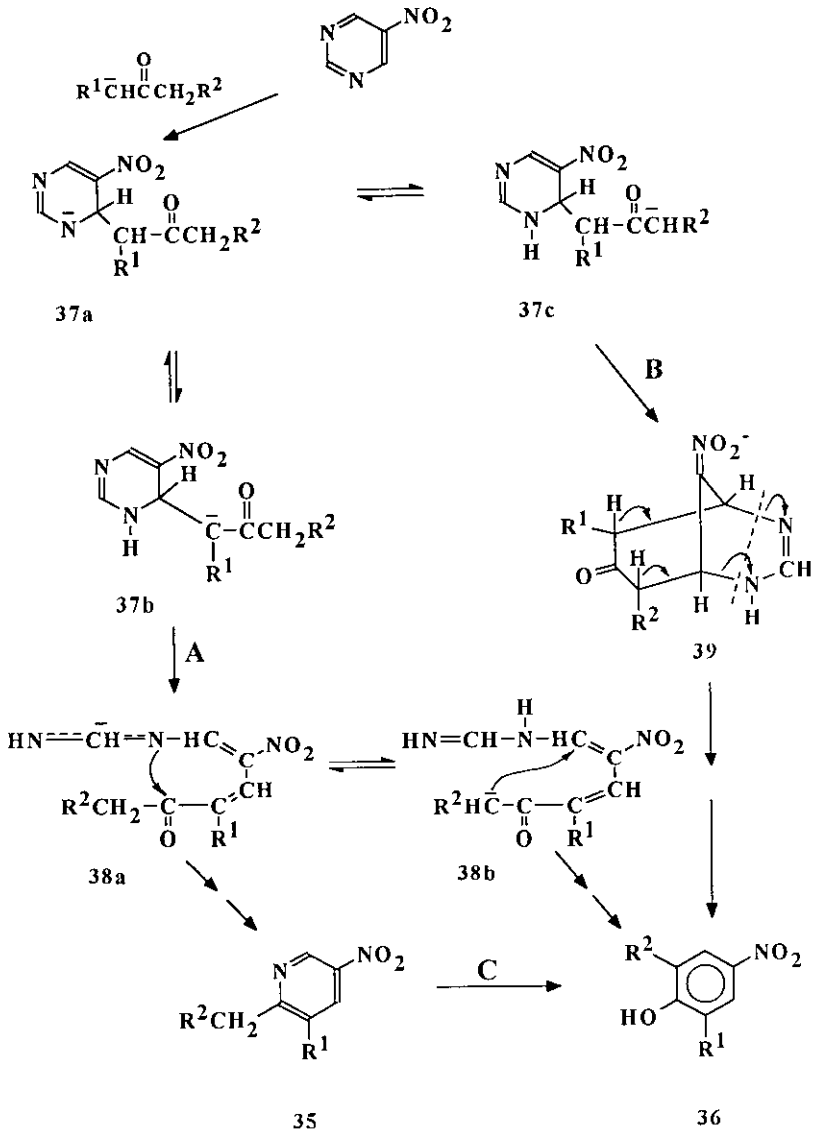
It is evident that in these reactions both the $N_{(1)}$-$C_{(2)}$-$N_{(3)}$ and the $N_{(1)}$-$C_{(2)}$ fragments of the pyrimidine ring are substituted by three or two carbon atoms of the reagents used. It is only in the reaction of 5-nitropyrimidine with dibenzyl ketone in diethylamine/ethanol that three fragments *i.e* the $N_{(1)}$-$C_{(2)}$-$N_{(3)}$, the $N_{(1)}$-$C_{(2)}$ as well as the $C_{(5)}$-$C_{(6)}$-$N_{(1)}$ fragment of the pyrimidine ring are substituted by fragments of the reagent, leading to a mixture of **35** (R = Ph), **36** (R = Ph) and **31**

The possible pathways for these conversions are shown in Scheme 18.

It is a rather complex picture and it is difficult to give priority to one of the mechanisms proposed It should be noted that in the reactions of 5-nitropyrimidines with CH-nucleophiles adduct formation at $C_{(4)}$ is thermodynamically favoured.[27] Therefore in the basic medium the formation of an equilibrium among the anionic σ-adducts (**37a** ⇌ **37b** ⇌ **37c**) may be proposed In route A the reaction proceeds with a ring-opening into open-chain intermediates (**38a** ⇌ **38b**) and cyclization into **35** and **36** respectively. In pathway B an internal attack of the carbon nucleophile in the side-chain of **37c** takes place leading to the formation of bicyclic adduct (**39**). Judging the results described in reference[25] that pyridines (**35**) are mainly formed at higher temperatures and in the presence of a weak base, and that at a lower temperature and in the presence a strong base 4-nitrophenols (**36**) are formed, seems to favor mechanism B for the phenol formation On the other hand, taking into consideration the rather severe conditions of the reaction we cannot exclude the formation of

4-nitrophenols as a result of a rearrangement of the 3-nitropyridine (**35**) into 4-nitrophenol (**36**) (route C),[26] making the reaction pathway pattern even more complex.

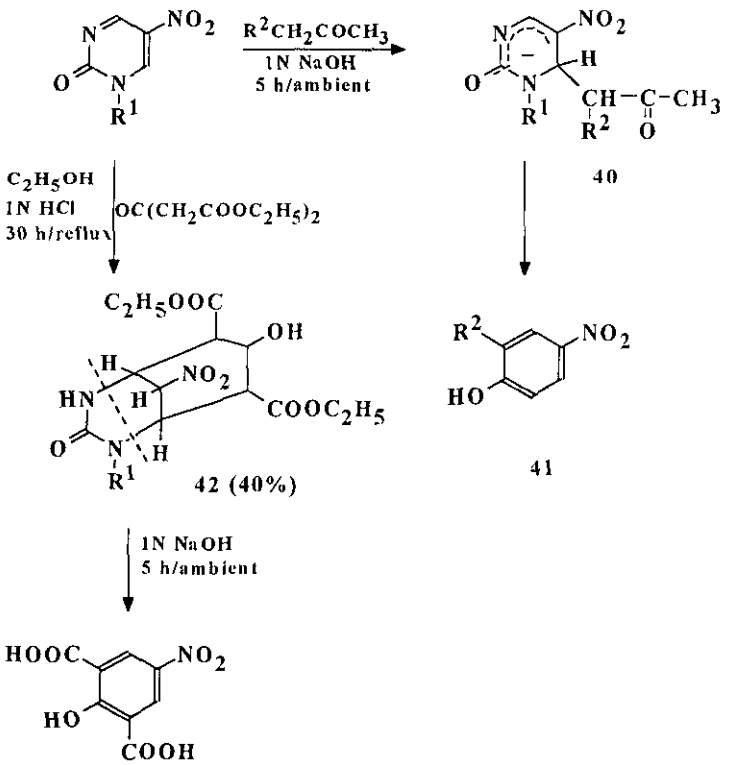
Scheme 18



Another example of pyrimidine-benzene ring transformations by replacement of the $N_{(1)}$-$C_{(2)}$-$N_{(3)}$ fragment for the three carbon chain of the nucleophile is the conversion of 5-nitropyrimidin-2-one by acetone in the

presence of a base, the corresponding 4-nitrophenols (**41**) being obtained (Scheme 19) [8] The formation of the 4-nitrophenols can proceed *via* the $C_{(4)}$-adduct (**40**) or a bicyclic adduct, such as **39** The observation that a bicyclic adduct (**42**) could be isolated when carbonyl substituted acetone derivatives, such as the diethyl ester of acetone dicarboxylic acid, were used supports the possible intermediacy of bicyclic adducts in the reaction of 5-nitropyrimidine with ketones (see Scheme 18).

Scheme 19

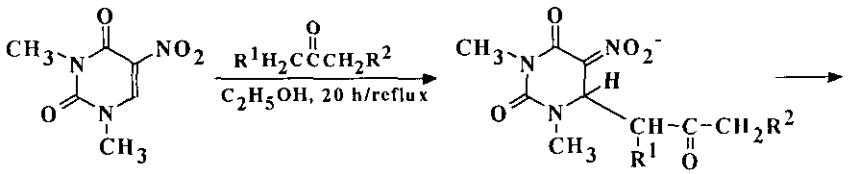


R^1	R^2	Yield **41**, %
H	H	85
H	Me	quantitative
Me	H	quantitative
H	COOEt	70

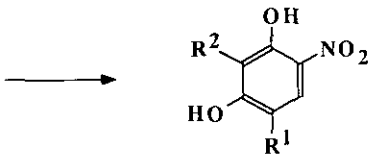
5-Nitrouracil derivatives show a decrease in electrophility at $C_{(6)}$ and a lower tendency to addition Adducts obtained are rather stable and less inclined to ring opening. Indeed, conversion of σ-adducts (**42**) obtained by

treatment of 5-nitro-1,3-dimethyluracil with ketones into resorcin derivatives require rather severe conditions and occurs in low yields (Scheme 20).[8, 9]

Scheme 20



42

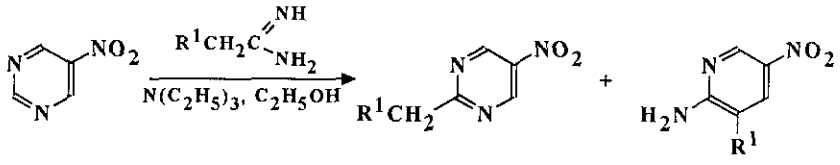


R^1	R^2	Yield, %
H	H	12
Me	H	27
H	Me	13
COOEt	H	11

Conversions proceeding formally with replacement of the three atom fragment $N_{(1)}$-$C_{(2)}$-$N_{(3)}$ of the pyrimidine ring by the N-C-N moiety of an amidine has been reported to occur during a three-hours reflux of an ethanolic solution of 5-nitropyrimidine with benzamidine hydrochloride or *tert*-butylamidine in the presence of triethylamine, affording 2-phenyl- or 2-*tert*-butyl-5-nitropyrimidine in 84 and 87% yields respectively. For a review on these so-called "degenerate" ring transformations see references 28-30

By extension of these studies using the CH-active amidines [R^1-CH_2-C(=NH)NH_2, R^1 = Me, Et] it was found that 5-nitropyrimidine undergoes besides the degenerate ring transformation into the 2-substituted 5-nitropyrimidines (**43**) also ring transformation into the 2-amino-5-nitropyridines (**44**) (Scheme 21) With phenylacetamidine 2-amino-3-phenyl-5-nitropyridine (**44**) (R^1 = Ph) is obtained as sole product

Scheme 21



43 44

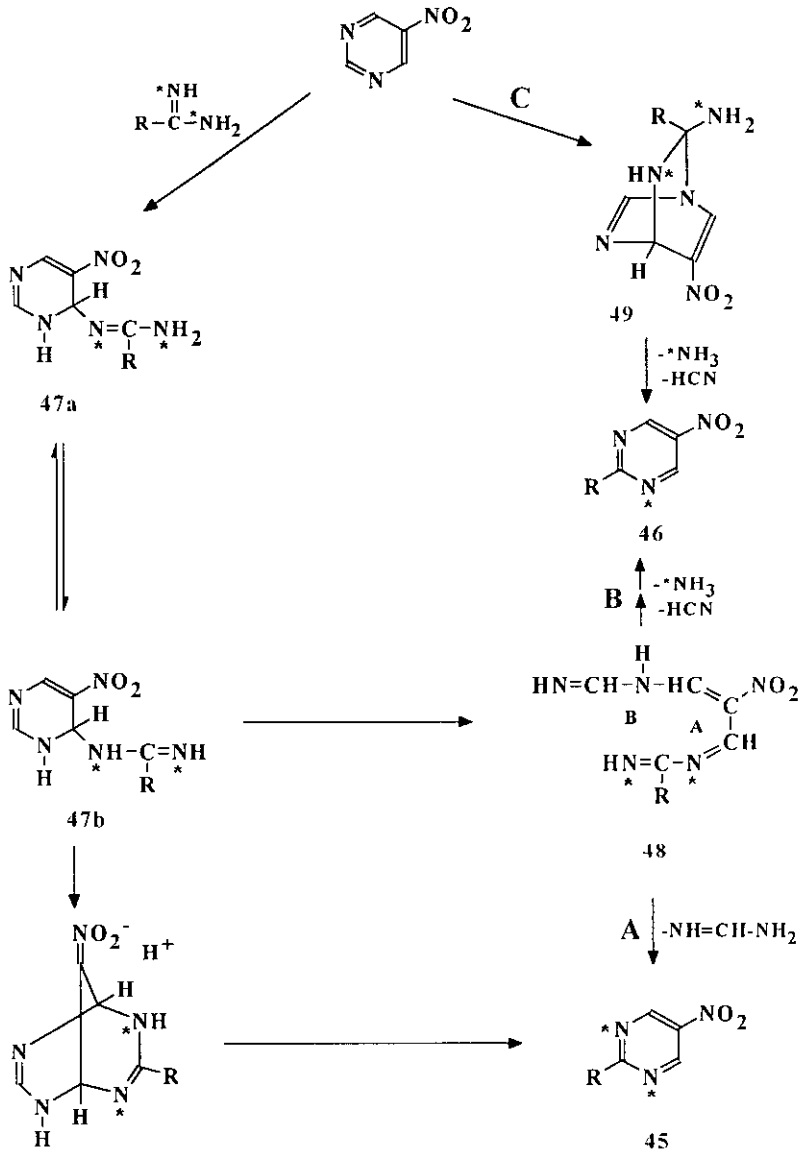
R^1	Conditions	Product (yield, %)
H	3 h/reflux	**43** (46) + **44**(11)
Me	3 h/reflux	**43** (30) + **44**(33)
Ph	2 h/0°C	**44** (57)
	0.25 h/reflux	**44** (86)

Experiments with ^{15}N-labelled amidines have shown [29] that a mixture of 2-R-5-nitropyrimidines is formed, i e. **45** , containing two labelled nitrogen atoms in the pyrimidine ring and **46** , containing only one ^{15}N-labelled nitrogen atom (Scheme 22) This means that the reaction proceeds according to two pathways and that apparently the amidine is able to act as donor of both N-C-N and C-N fragments In case of benzamidine, both compounds are formed in nearly equal yields [44% of **45** (R = Ph) and 56% of **46** (R = Ph)] This reaction can be described to follow an ANRORC-mechanism involving an initial nucleophilic attack of the amidine nitrogen atom at the 6-position of 5-nitropyrimidine (see Scheme 22), leading to σ-adduct (**47a** ⇌ **47b**).

The formation of **45** and **46** can be explained *via* the open chain intermediate (**48**); cyclization of **48** according to reaction pathway A gives **45** , while cyclization of **48** into compound (**46**) is described in pathway B

Since 5-nitropyrimidine has been found [31] to undergo easily ($4\pi + 2\pi$) cycloaddition reactions with an inverse electron demand, another pathway can be postulated, *i.e.* the electron-rich benzamidine gives a regiospecific cycloaddition across the $N_{(1)}$ and $C_{(4)}$ position of 5-nitropyrimidine leading to the intermediacy of 8-R-8-*N*-amino-6-nitro-7-*N*-2,4,7-triazabicyclo[2 2.2]octa-2,5-diene (**49**) (pathway C) By loss of ^{15}N-labelled ammonia and hydrogen cyanide (**46**) is formed. The fact that **46** only contains half of the ^{15}N being present in the benzamidine is not contradictory to this view

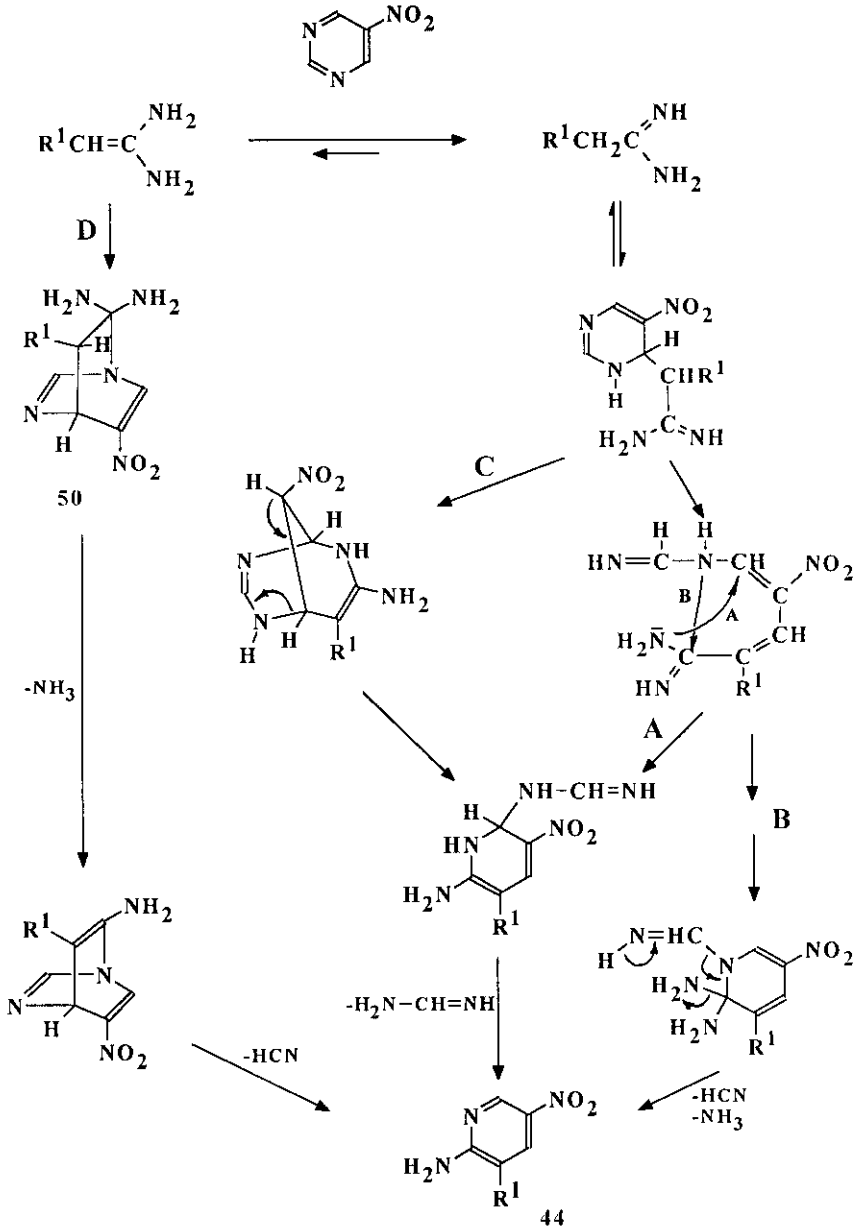
Scheme 22



The formation of the 2-substituted 5-nitropyrimidines (**43**) from 5-nitropyrimidine with R^1-$CH_2C(=NH)NH_2$ (R^1 = Me, Et) can be explained in a similar way (Scheme 22), *i.e.* involvment of the σ-adduct (**47**) (R = Me, Et) and/or the intermediate formation of cycloadduct (**49**) (R = Me, Et).

The formation of 2-amino-3-R^1-5-nitropyridine (**44**) seems more complex; different pathways can be proposed (Scheme 23) [28]

Scheme 23



In one of the pathways an σ-adduct at C_6 can be postulated, in which not the amidine nitrogen, but the α-carbon of the amidine is attached to position 6. This σ-adduct can undergo ring-opening into an open-chain intermediate which undergoes ring closure according to pathway A or B. In pathway A the pyridine ring contains the N-C-C fragment of the amidine (thus it reacts as N-C-C donor), in pathway B it is only the C-C fragment of the amidine, which is incorporated into the pyridine ring (thus the amidine reacts as C-C donor). An alternative way for the σ-adduct to react is an internal cyclization into the bicyclo adduct which by further rearrangement gives **44** (pathway C).

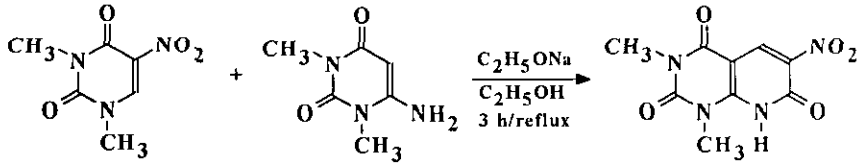
Use of the ^{15}N labelled phenylacetamidine and detailed nmr studies of the reaction mixture substantiate that C-substituted derivatives of acetamidine can indeed act both as C-C-N or C-C donor causing replacement of the $N_{(1)}$-$C_{(2)}$-$C_{(3)}$ or $N_{(1)}$-$C_{(2)}$ fragments of the pyrimidine ring correspondingly (Scheme 23, pathways A, B or C)

Results of our studies on cycloaddition reactions of 5-nitropyrimidine by action of dienophiles, such as diamino- and dialkoxyolefins or enamines[31] suggest another possible pathway, i e pathway D involving the formation of the 1,4-cycloaddition product (**50**) in the reaction with CH-active amidines. By loss of ammonia and hydrogen cyanide the aminonitropyridine (**44**) is formed

The presence of *N*-substituents in phenylacetamidine considerably decreases the rate of the reaction When *N,N*-dimethylphenylacetamidine interacts with 5-nitropyrimidine besides 2-dimethylamino-5-nitro-3-phenylpyridine, the de-dimethylated product *i.e.* 2-amino-3-phenyl-5-nitropyridine was obtained. With *N,N*-diethylphenylacetamidine no de-ethylation occurs, only 2-diethylamino-5-nitro-3-phenylpyridine is obtained

An interesting example of $N_{(1)}$-$C_{(2)}$-$N_{(3)}$ replacement by the C-C-N of the amidine has been reported to take place in the reaction of 5-nitro-1,3-dimethyluracil with 1,3-dimethyl-6-aminouracil which can formally be regarded as a cyclic amidine.[34] The reaction resulted in 6-nitropyrimidine[4,5-*b*]pyridine-2,4,8-trione (**51**) (Scheme 24).

Scheme 24

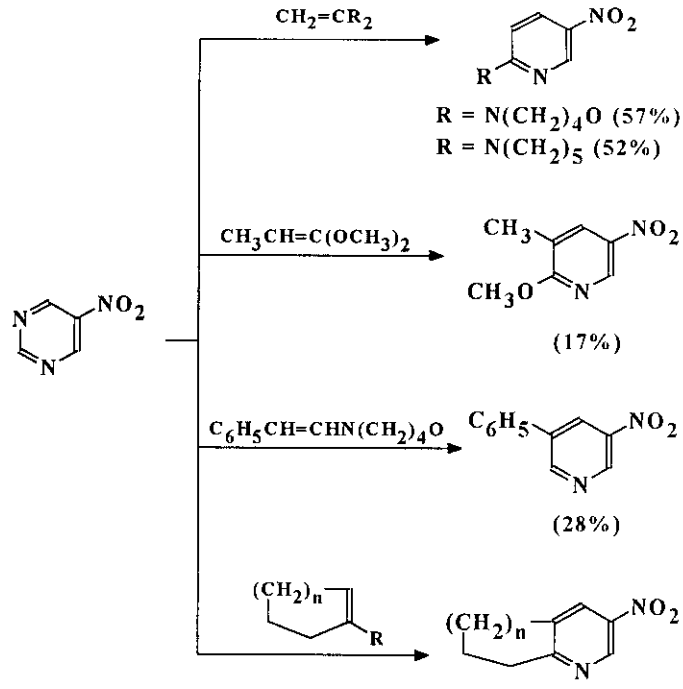


51

Yield 34%

Interesting series of ring transformations are reported to occur when 5-nitropyrimidine participates in an inverse electron-demand [4 + 2] cycloaddition reaction with electron-rich olefins, the olefins react as dienophiles and the 5-nitropyrimidine acts as an electron-deficient azadiene.[31, 35, 36] Interaction of 5-nitropyrimidine with a variety of *N,N*- and *O,O*-ketene acetals or enamines is found to be regioselective and leads to the formation of 2-mono- or 2,3-disubstituted 5-nitropyridines (Scheme 25). The overall-reaction describes the replacement of the $N_{(1)}$-$C_{(2)}$ fragment by two carbons of the dienophile. As one can see from the reactions presented in Scheme 25, this route opens an easy access to a number of differently substituted pyridines and especially to compounds, in which carbocyclics are b-fused with pyridines (Scheme 25)

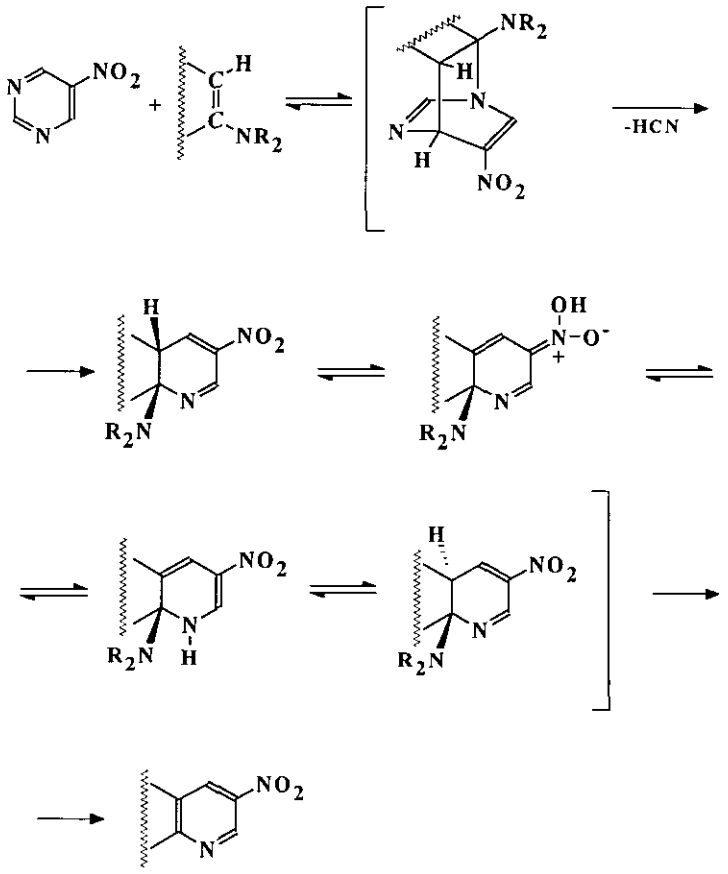
Scheme 25



n	R	Yield, %
1	$N(CH_2)_4O$	60
2	$N(CH_2)_4O$	80
1	$N(CH_2)_5$	60
2	$N(CH_2)_5$	80
3	$N(CH_2)_5$	75
4	$N(CH_2)_5$	76

The substitution pattern in the 3-nitropyridines obtained suggests the intermediacy of a 1,4-cycloadduct being formed by addition of the unsubstituted carbon of the dienophile to $C_{(4)}$ of the 5-nitropyrimidine, and of the carbon bearing the electron-donating group, to $N_{(1)}$ of the pyrimidine ring (Scheme 26). The observed regioselectivity is supported by calculations using the FMO-pertubation theory.[35]

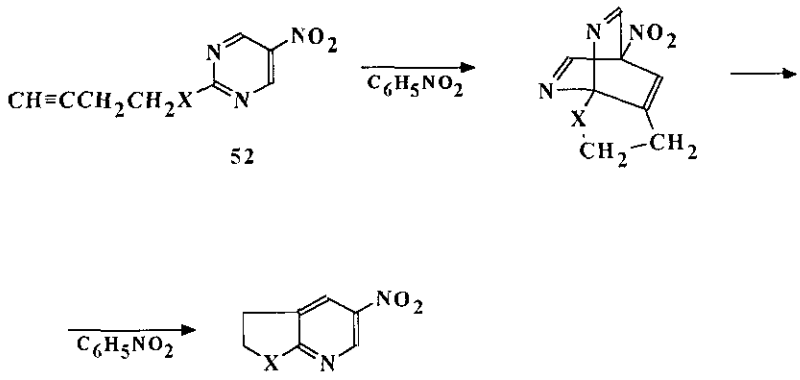
Scheme 26



Carbocyclic and heterocyclic rings being b-fused to the pyridine ring are also formed in high yields when heating a solution of 5-nitropyrimidines, containing at position 2 a side chain with an ω-triple bond, in nitrobenzene (Scheme 27). The formation of these products can be explained by an *intra*molecular Diels-Alder cyclization of the triple carbon-carbon bond in (**52**) to the $C_{(2)}$ and $C_{(5)}$ position (see Scheme 27) and a

subsequent expulsion of hydrogen cyanide [37, 38] This *intra*molecular cyclization is strongly supported by the entropic assistance of the tethering chain between the azadiene and the dienophile in **52**

Scheme 27

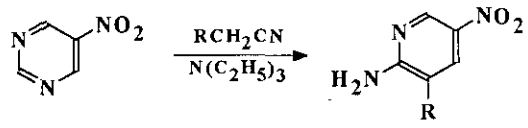


X	Conditions	Yield, %
O	24 h/reflux	55
S	24 h/reflux	75
NAc	24 h/180C°	87
$C(CN)_2$	12 h/180C°	96

The replacement of the $N_{(1)}$-$C_{(2)}$ fragment of the pyrimidine ring by a C-C fragment also takes place in reactions of CH-active nitriles (Scheme 28) [37] Unsubstituted phenylacetonitrile, unlike phenylacetamidine, does not react with 5-nitropyrimidine, but arylacetonitriles bearing electron withdrawing substituents (CF_3, NO_2, CN) in the benzene ring proved to be effective reagents to cause the formation of products (**53**) Malononitrile, phenylsulfonylacetonitrile and cyanoacetic esters give similar reactions The reaction course can be described according to pathway B in Scheme 23.

In a similar way the pyrimidine ring present in pteridines[39] or purines[40-42] is transformed into a pyridine ring by reaction with acetonitrile. Quaternization of the pyrimidine ring activates this ring transformation process [43, 44]

Scheme 28



53

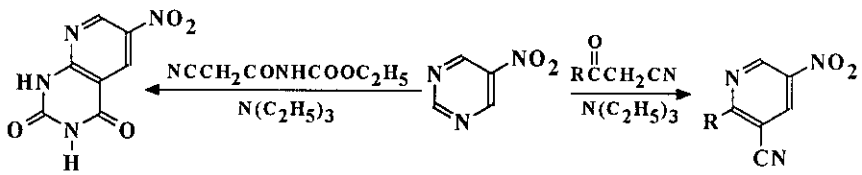
R	Conditions	Yield, %
Ph	CD_3OD, 4 h/reflux	0
C_6H_4-CF_3-m	EtOH, 2 h/60°C	20
C_6H_4-NO_2-p	EtOH, 2 h/70°C	65
CN	MeOH*, 20 h/20°C	66
SO_2Ph	EtOH, 2 h/70°C	75
COOMe	MeOH, 2 h/reflux	17
	EtOH, 2 h/reflux	26
COOEt	EtOH, 1 h/20°C	0
	EtOH, 2 5 h/70°	65
$COOCMe_3$	MeOH, 2 h/20°C	67
	EtOH, 2 5 h/70°C	0
$CONR^2$	MeOH, 1 h/10°C	0
	MeOH, 90 h/20°C	55

*without triethylamine

The successful reaction of 5-nitropyrimidine with CH-active acetonitriles allows one to introduce substitutions into position 3 of 2-aminopyridine, which may be used for further syntheses For instance, the reaction of 5-nitropyrimidine with *N*-(cyanoacetyl)carbamate affords 1,2,3,4-tetrahydro-6-nitropyrido[2,3-*d*]pyrimidine-2,4-dione in high yield (Scheme 29)

β-Ketonitriles ($RCOCH_2CN$) also react with 5-nitropyrimidine quite easily In this reaction there is an interesting participation of the C=O group and not of the nitrile group in the cyclization of the intermediary open-chain intermediate resulting in the formation of 3-cyano-5-nitropyridines (**54**) When R = OMe, besides the main product (**53**) (R = COOMe), a small amount of 3-cyano-5-nitro-2(1*H*)-pyridone (**60**) is obtained

Scheme 29



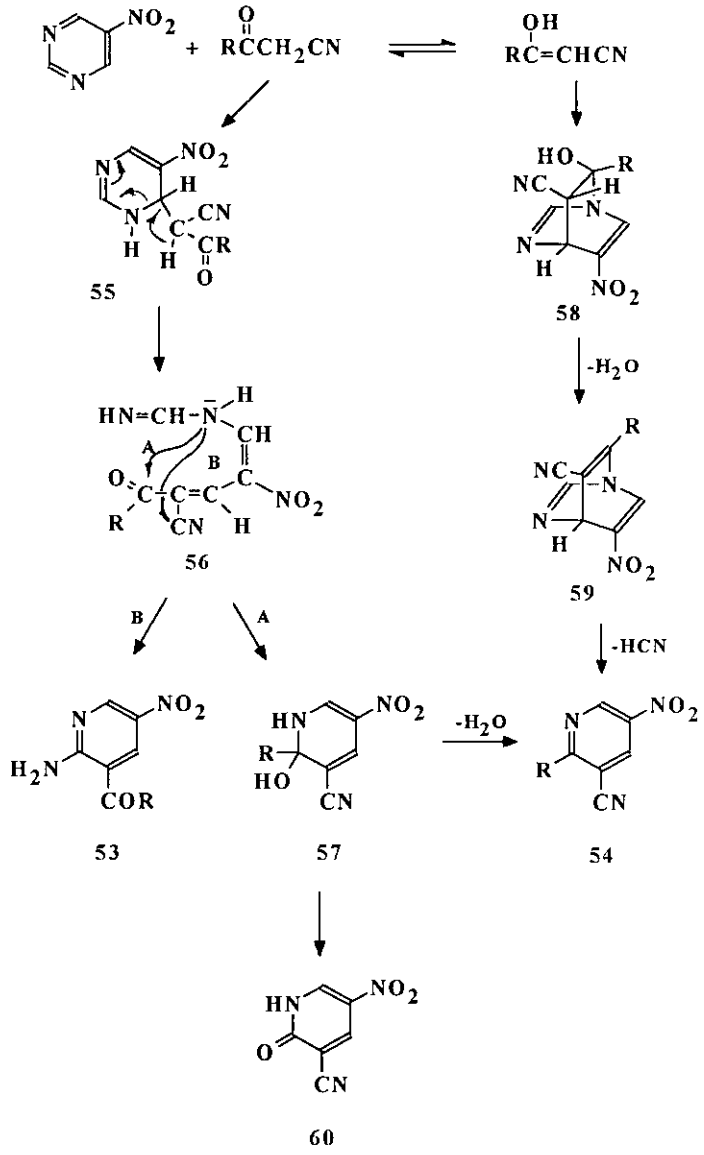
(84%) 54

R	Conditions	Yield, %
Me	EtOH, 2 5 h/reflux	13
Ph	EtOH, 2.5 h/60°C	62

Taking into consideration the results of previous studies two plausible mechanism can be advanced for the formation of product (**54**) (Scheme 30). One reaction pathway describes a process in which the reaction proceeds *via* the open-chain intermediates (**56**), obtained by ring opening of σ-adduct (**55**), followed by an intramolecular cyclization through the addition of the amidine nitrogen to the carbonyl group yielding the 1,2-dihydropyridines products (**57**) (pathway A). Elimination of water forms product (**54**). Alternatively product (**54**) can also be suggested to be formed according to an inverse type Diels-Alder cycloaddition involving the tautomeric enol and the electron-deficient 5-nitropyrimidine Elimination of water from cycloadduct (**58**) gives **59** , from which by a retrodiene process **54** is formed (Scheme 30) In the same scheme the formation of products (**53**) and (**60**) is explained.

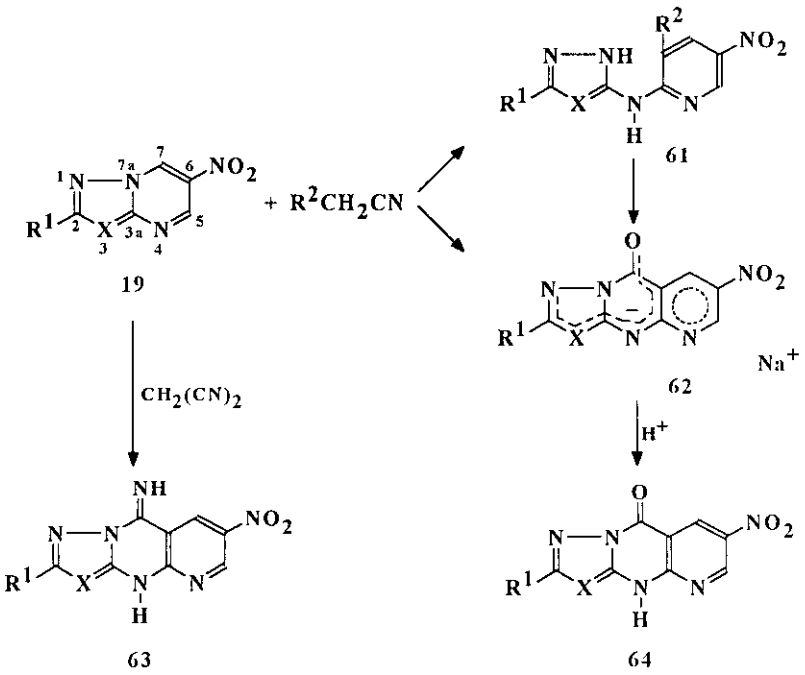
6-Nitroazolo[1,5-*a*]pyrimidines undergo by action of CH-active acetonitriles an interesting ring transformation reaction, being different from that observed with the monocyclic 5-nitropyrimidines [45-51] Half an hour reflux of an ethanolic solution of a great number of 2-substituted 6-nitrotriazolo[1,5-*a*]pyrimidines (**19**) [R^1 = H, Me, SMe, CF_3, Cl, NH_2, NMe (X = N)] with ethyl cyanoacetate, cyanoacetamide, cyanothioacetamide, benzoylacetonitrile results in the formation of 2-(5-R^1-1,2,4-triazolylamino)-3-R^2-5-nitropyridines (**61**), the structure of which was proved by X-ray analysis (Scheme 31). The reaction proceeds without any activation of both reagent and substrate and the majority of the products are formed in good yields Compounds (**19**) containing electron-donating groups in the triazole ring (R^1 = NH_2 and NMe) have a reduced reactivity and require a higher temperature and extended reaction time (heating at 100° C in DMF) for two hours.

Scheme 30



6-Nitropyrazolo[1,5-*a*]pyrimidine (**19**) (X = CH) itself is unreactive, but after introduction of electron-withdrawing substituents in the pyrazole ring (X = CCOOEt, X = CNO_2) compounds (**19**) undergo conversion into the pyrazoloaminopyridines (**61**) [46, 48]

Scheme 31



19 61 62 63 64

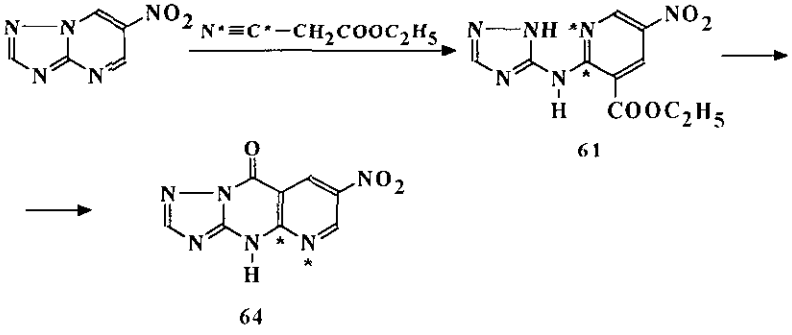
R1	X	R2	Conditions	Product (Yield, %)
H	N	COOEt	EtOH, 0 5 h/reflux	**61** (54)
			Na_2CO_3, EtOH, 0 5 h/reflux	**62** (98)
CF_3	N	COOEt	EtOH, 0.5 h/reflux	**61** (64)
			Na_2CO_3, EtOH, 0.5 h/reflux	**62** (97)
NMe_2	N	COOEt	DMF, 2 h/reflux	**61** (49)
H	CCOOEt	COOEt	EtOH, 0.5 h/reflux	**61** (48)
			Na_2CO_3, EtOH, 0 5 h/reflux	**62** (96)
H	N	$CONH_2$	EtOH, 0 5 h/reflux	**61** (61)
			Na_2CO_3, EtOH, 0 5 h/reflux	**62** (90)
CF_3	N	$CONH_2$	EtOH, 0.5 h/reflux	**61** (61)
NMe_2	N	$CONH_2$	DMF, 2 h/reflux	**61** (60)
H	CCOOEt	$CONH_2$	EtOH, 0 5 h/reflux	**61** (48)
H	N	$CSNH_2$	EtOH, 0.5 h/reflux	**61** (56)
H	N	CN	EtOH, 0.5 h/reflux	**63** (98)
CF_3	N	CN	EtOH, 0.5 h/reflux	**63** (90)
NMe_2	N	CN	EtOH, 0 5 h/reflux	**63** (87)
H	CCOOEt	CN	EtOH, 0.5 h/reflux	**63** (95)

Attempts to increase yields of the compounds (**61**) by activation of the acetonitriles through the conversion into anions did not lead to product (**61**) but to the 7-nitro-9-oxo-4,9-dihydroazolo[1,5-*a*]pyrido[2,3-*d*]pyrimidine salts (**62**) These salts were also obtained in nearly quantitative yields when the 2-triazolylaminopyridines (**61**) were heated in alkaline alcohol.

In the reaction of the 6-nitroazolo[1,5-*a*]pyrimidines (**19**) (X = N, CCOOEt or CNO_2) with malononitrile under mild conditions (reflux in alcohol) not **61** (R^2 = CN) but its tricyclic product, i e. 7-nitro-9-imino-4,9-dihydroazolo[1,5-*a*]pyrido[2,3-*d*]pyrimidine (**63**) is obtained (see Scheme 31) Apparently under the applied reaction conditions **61** (R^2 = CN) cyclises into **63** . Intermediate (**61**) is registered when the reaction is studied in nmr spectrometer [48]

A study of the ring transformation of **19** with ethyl cyanoacetate containing two isotopic labels (^{13}C and ^{15}N) in the nitrile group[48, 51, 52] showed that in both compounds (**61**) and (**64**) the $N_{(1)}$-$C_{(2)}$ fragment of the pyridine ring is formed from the cyano group of the reagent (as proved by ^1H and ^{13}C nmr spectroscopy) (Scheme 32)

Scheme 32

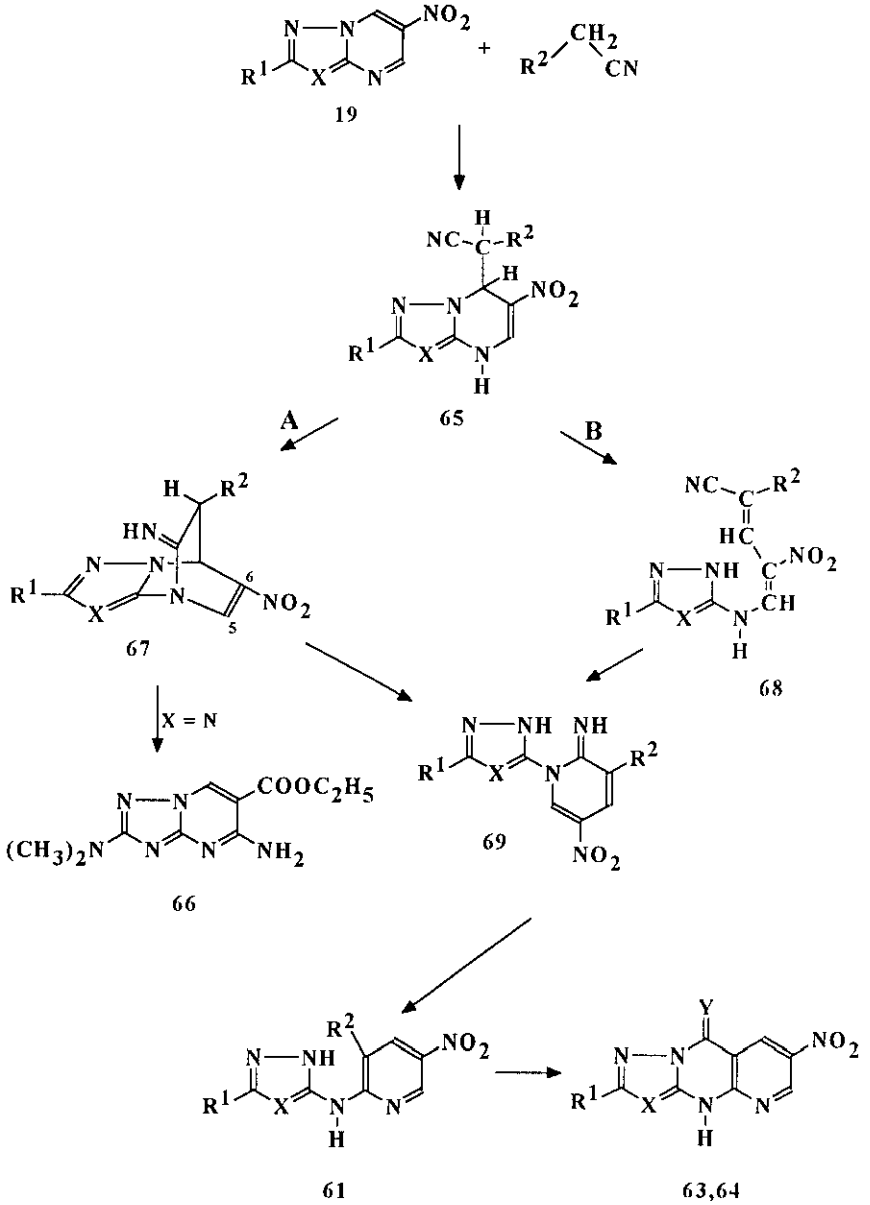


Nmr-study of the reaction of 2-dimethylamino-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidine (**19**) (X = N, R^1 = NMe_2) with ethyl cyanoacetate shows the intermediary formation of σ-adduct (**65**) (R^2 = COOEt) (Scheme 33).

It may be assumed that these adducts can be transformed into **69** *via* either an intermediary cyclo adduct (**67**) (pathway A) or open-chain compound (**68**) (pathway B) which on ring closure gives **69** In order to explain the results of the labelling experiments a Dimroth rearrangement of **69** into **61** is proposed Cyclisation

gives the compounds (**63, 64**) The possible intermediacy of **67** in the formation of **69** is substantiated by the fact that in the reaction of **19** (X = N, $R^1 = NMe_2$) with ethyl cyanoacetate together with the usual product (**61**) also 2-dimethylamino-5-amino-6-carbethoxy-1,2,4-triazolo[1,5-*a*]pyrimidine (**66**) has been isolated Its formation suggests elimination of the $C_{(5)}$-$C_{(6)}$ fragment (nitroacetylene?) from **67** (R^2 = COOEt)

Scheme 33



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