METHODS FOR THE SYNTHESIS OF 3-NITROPYRIDINES (REVIEW)

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The review includes the published data on methods for the synthesis of compounds that contain the 3-nitropyridine skeleton from acyclic synthones and via transformation of other heterocyclic rings.

The first publications regarding the synthesis of 3-nitropyridine derivatives were printed quite some time ago (for example, see [1]); however, the specific properties that are responsible for the unique possibilities of the use of these compounds in organic synthesis were discovered only recently. The introduction of a nitro group into the β position of the pyridine ring causes an increase in the π-deficient character of the heteroring, which leads to: 1) facilitation of attack by nucleophiles and subsequent transformations of the σ adducts (nucleophilic substitution and opening and transformation of the ring); 2) intensification of the CH acidities of the α- and γ-alkyl substituents, which leads to reactions of the side chains with electrophiles [3-10]. Other synthetic possibilities can be demonstrated in the case of variously planned reactions (including redox processes) of 3-nitropyridine derivatives with the CN^- ion (see [11] and the literature citations therein). It is precisely these properties that ensure the diversity of the synthetic utilization of 3-nitropyridine derivatives.

The methods used for the synthesis of structures that contain a 3-nitropyridine fragment can be divided into three large groups: the introduction of a nitro group into a pre-existing pyridine ring, production from acyclic synthones, and transformation of other heterocycles.

Information on methods for the synthesis of 3-nitropyridines has been correlated in four principal reviews [12-15]. Data on the direct nitration of the pyridine ring have been systematized in a monograph [12] and in a review [13]. It should be noted that the nitration of the π-deficient pyridine ring is limited to structures that contain several methyl [12] or donor functional groups [13] and will not be examined within the framework of this review, nor will indirect methods for the introduction of a nitro group. Data on the synthesis of 3-nitropyridines from acyclic fragments have been presented in previous reviews [14, 15], which were devoted to methods for the synthesis of nitro azines, and do not claim to be complete. In addition, not one of these reviews contains virtually any information on the production of 3-nitropyridines by the transformation of other heterocyclic structures, although constantly increasing attention has been directed to this problem in recent years.

1. SYNTHESIS OF 3-NITROPYRIDINE STRUCTURES FROM ACYCLIC SYNTHONES

The methods for the construction of the 3-nitropyridine skeleton from acyclic compound can be conveniently classified with respect to the type of C—C bond formed. This sort of classification can be represented by the following formal scheme (the pertinent sections of our review are indicated above the arrows) (see scheme below).

It should be noted that virtually all of the indicated variants for the construction of the 3-nitropyridine ring must be accompanied by the formation of C—N bonds; this matter will not be mentioned in what follows

1.1. Formation of the $C_{(3)}$—$C_{(4)}$ Bond

The formation of the $C_{(3)}$—$C_{(4)}$ bond is the most frequently encountered pathway for the construction of the 2-nitropyridine ring, as well as more complex structures containing a 3-nitropyridine fragment.

Nitro-containing synthones that are donors of a two-carbon fragment are represented primarily by vicinal amino nitro alkanes, α-nitro carbonyl compounds, and nitroacetic derivatives. The second, three-carbon fragment that is necessary for the construction of the pyridine skeleton includes derivatives of β-dicarbonyl compounds or α,β-unsaturated carbonyl compounds. It is essential that both fragments may be both strictly carbonyl compounds and derivatives of them with the same oxidation state (for example, enamines for carbonyl compounds, esters, amides,

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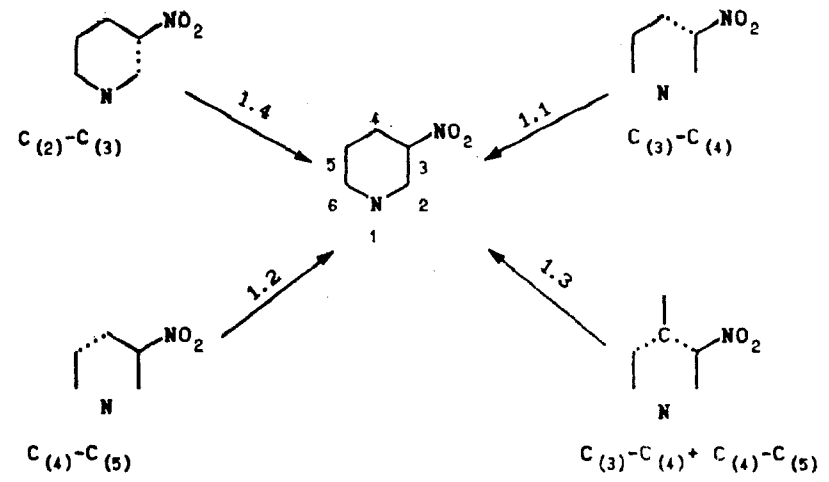
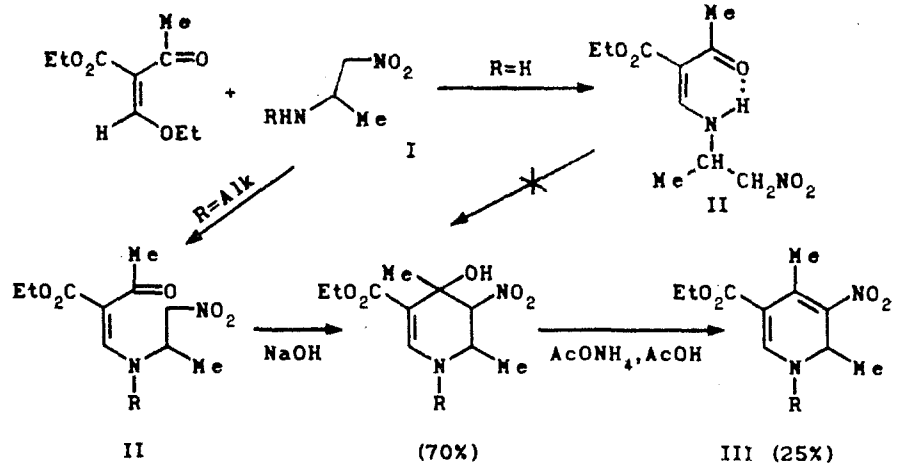
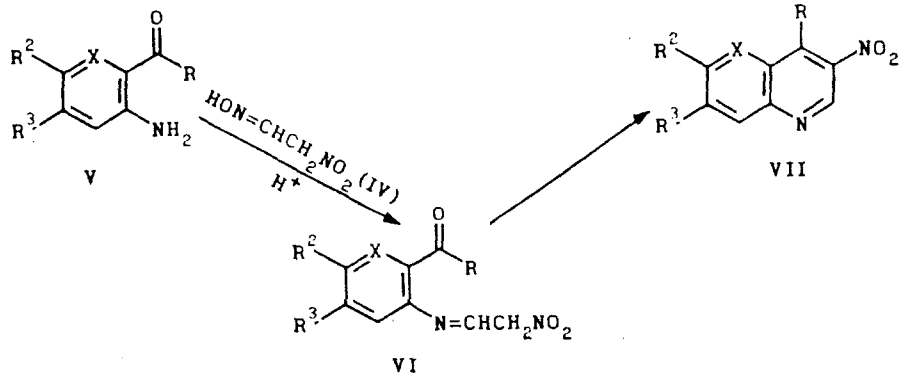


and ketene aminals or ketene dithioaminals etc. for acids). o-Acyl(or carboxy)anilines or vic-acylaminoheterocycles generally serve as the three-carbon fragments for the synthesis of condensed 3-nitropyridine derivatives.



The simplest representatives of two-carbon nitro synthones are vicinal amino nitro alkanes I, the condensation of which with ethoxymethyleneacetoacetic ester gives α,β-unsaturated amino ketones II. The intramolecular cyclization of tertiary amino ketones II (R = Alk) leads, after dehydration, to dihydropyridines III, while secondary amino ketones II (R = H) are stable under cyclization conditions [16].

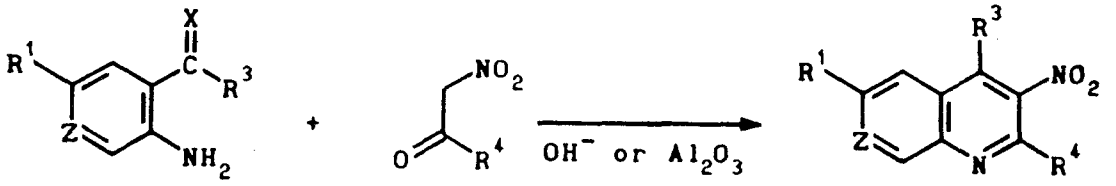
α-Nitro carbonyl compounds have found much wider application in synthetic practice. Thus the condensation of the readily accessible metazonic acid (nitroacetaldehyde oxime) (IV) with o-acylanilides V (X = C—R^1, R = H, Alk, Ar) leads to Schiff bases VI, which are then cyclized to 3-nitroquinolines VII by the action of dilute alkalis or activated Al_2O_3 [17-24].



All unindicated R=H, the yields of the products for the reaction in dilute NaOH: X=C—R^1, R=Me (92%); R^1=NO_2 (0%); R^2=NO_2 (0%); Cl (86%); Me (54%); R^3=NO_2 (0%); Cl (50%); R^2=R^3=Me (55%); MeO (32%); R^2+R^3=$(CH_2)_3$

Schiff bases VI, which contain nitro groups in various positions of the benzene ring, undergo cyclization in quantitative yields only on Al_2O_3 [22]. A similar reaction of metazonic acid with anthranilic acid or its esters V (X = C—R^1, R = OH, OAlk) leads to 4-(hydroxy(alkoxy)-3-nitroquinolines VII (R = OH, OAlk), the only difference being that the cyclization takes place under severe conditions [25-29]. Also possible is the use of 3-aminopicolinic acid V (X = N, R^2 = R^3 = H), as a result of which 3-nitro-1,5-naphthyridines are obtained [30].

In contrast to nitroacetaldehyde, which is stable only in dilute solution and is used in the oxime form (metazonic acid), stable (in the free form) α-nitro ketones readily condense with o-aminocarbonyl aromatic compounds (or their Schiff bases) and form 2-substituted 3-nitroquinolines [31, 32].

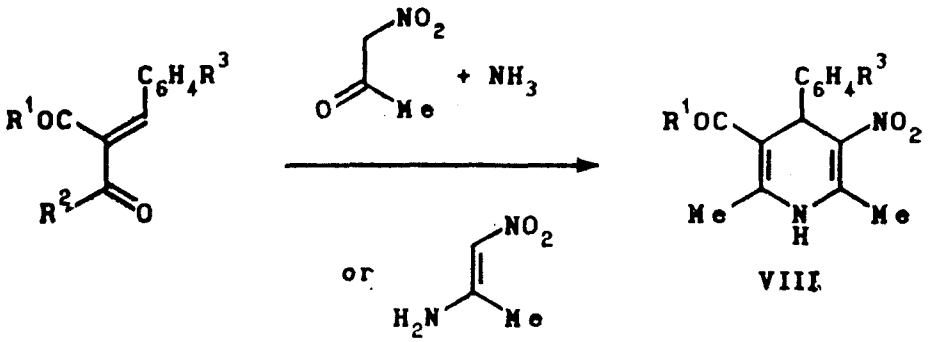


X=O, p-MeC$_6$H$_4$N; Z=CR^2,N

Z=C—R^2: R^1=R^2=R^3=H, X=O, R^4=Me (69%) [31], Ph (54...61%) [32], *p*-RC_6H_4, R=Cl (55%), Me (17%), MeO (25%), NO_2 (38%) [32]; R^1+R^2=O(CH_2)O, R^3=H, R^4=Me, X=O (52%) [31]; R^1=R^2=H, R^3=Ph, R^4=Me, X=O (63%) [32]; X=*p*-MeC_6H_4N, R^1=R^2=R^3=H, R^4=Ph (47...56%), *p*-ClC_6H_4 (41%) [32]

The similar cyclization of N-(3-amino-4-picolidene)-p-toluidine (Z = N) with ω-nitroacetophenone in refluxing alcohol gives 3-nitro-2-phenyl-1,7-naphthyridine in only 10% yield [33].

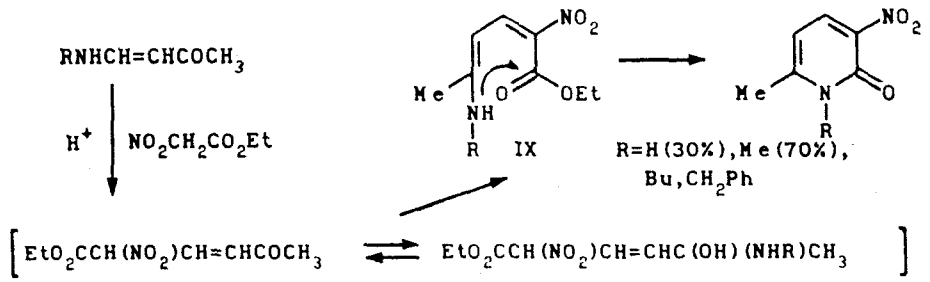
The use of α,β-unsaturated ketones as the three-carbon fragment in the condensation with nitroacetone or its enamine leads to substituted 3-nitro-1,4-dihydropyridines [34-40]. It is noteworthy that information on this class of compounds has been published almost exclusively in the voluminous patent literature. This is due to the extensive prospects for the use of dihydropyridines VIII in medical practice as ligands of Ca channels (for example, see [41]), heart-rhythm regulators, and agents that affect the circulatory system and thrombocyte aggregation.



VIII

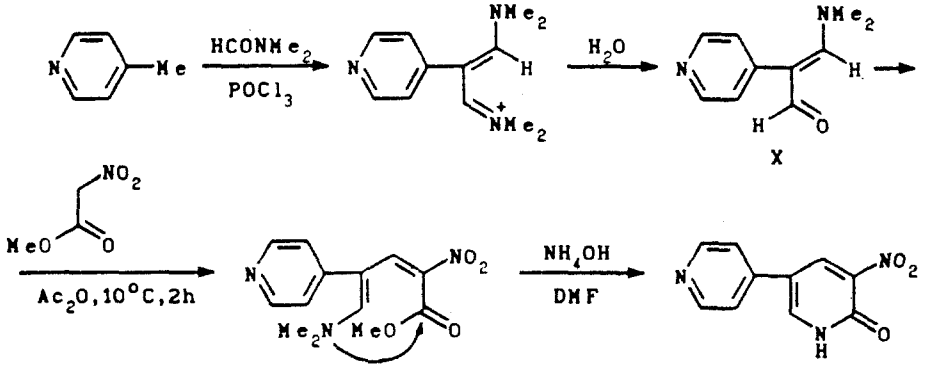
The expansion of the radicals is presented in Sec. 1.3.

Replacement of the nitro ketones by nitroacetic acid derivatives leads to 3-nitro-2-pyridones [42, 43]:

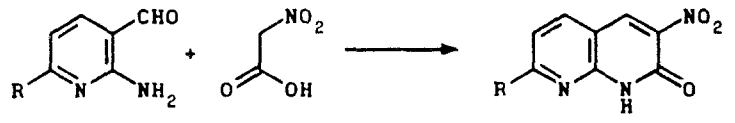


In the case R = Bu, intermediate diene IX was isolated and was cyclized to a pyridone by heating in alcohol [42].

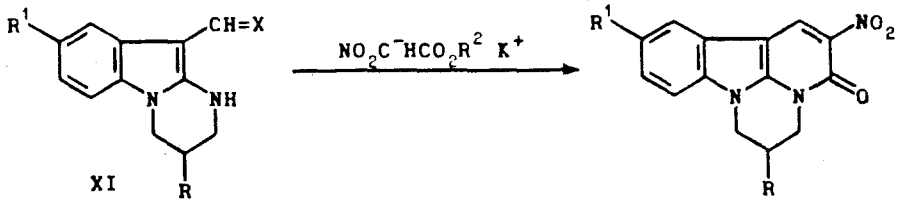
The original method for obtaining the starting hetaryl-substituted enamino carbonyl compounds consisted in the Vilsmaier diformylation of the CH-acid methyl groups of π-deficient nitrogen heterocycles with subsequent hydrolysis to enamino aldehyde X. The condensation of the latter with nitroacetic ester leads to 5-(4-pyridyl)-3-nitro-2-pyridone [44].



o-Amino aldehydes of the pyridine [45] and indole [46, 47] series, which formally contain an enamino carbonyl fragment, react with nitroacetic acid or its ester to give heteroannelated 3-nitro-2-pyridones. The formyl group of indole, however, requires activation.



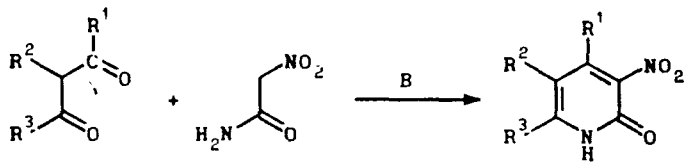
R=H(74%); R=Ph(47%)



X=N+Me2; O

R=R1=H(70%); R=Me,R1=H(73%)
R=Me,R1=Br(85%)

β-Dicarbonyl compounds are usually utilized in the condensation with nitroacetic acid amides to obtain 3-nitro-2-pyridones [48, 49].



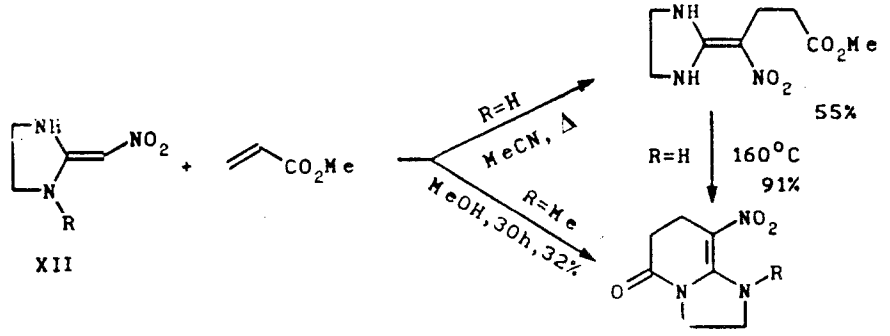
R^1=H, R^2=R^3=Me, B — piperidine acet. (89%) [48]; R^1=CO_2Et, R^2=H, R^3=Me, B=Et_2NH (13%) [49]

TABLE 1. Conditions for the Conversion of Nitro Ketene Aminals by the Action of Alkenals

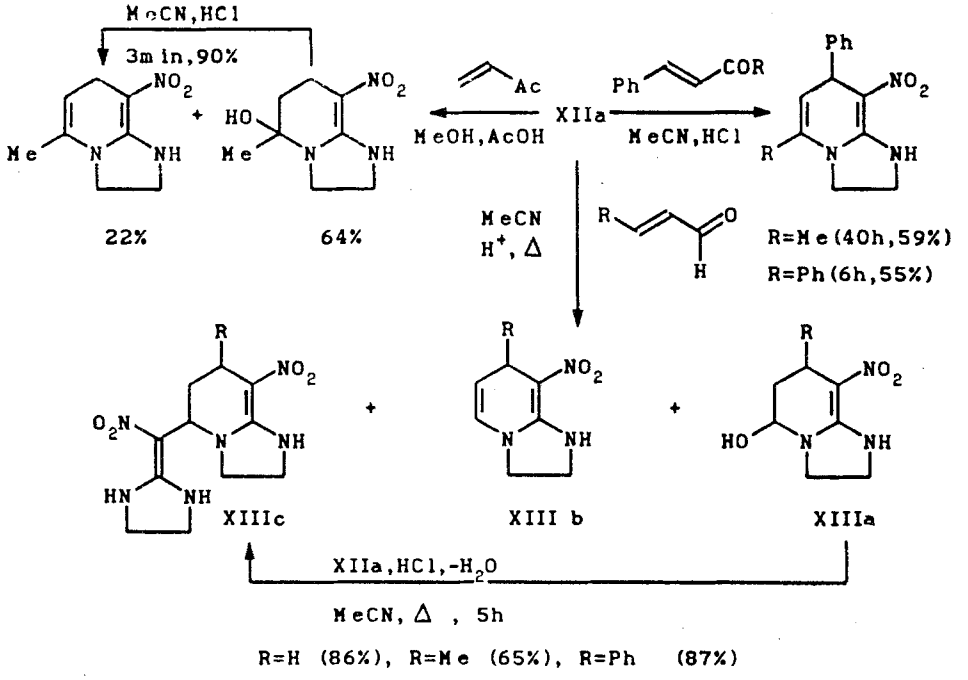
R	Catalyst	Reaction time, h	Yield, %		
			XIII a	XIII b	XIII c
H	HCl	8*	56	35	—
Me	AcOH	15	63	—	—
Me**	HCl	8	—	16	52
Ph	AcOH	24	33	—	—
Ph	HCl	8	6	6	87

*Using two equivalents of XIIa.
**Reaction temperature 40°C.

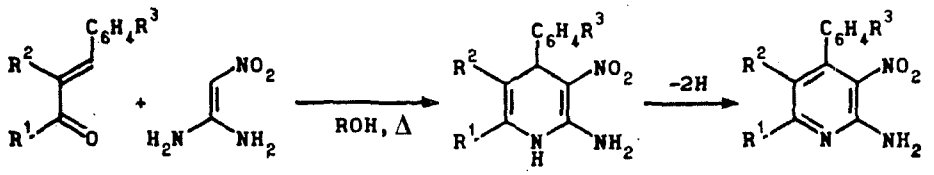
Nitro-substituted ketene aminals are very convenient synthones for obtaining nitrogen heterocycles in reactions with 1,3-biselectrophiles with various structures. Cyclic β-nitro ketene aminals — imidazolidine derivatives — react with α,β-unsaturated carbonyl compounds to give primarily condensed 1,4-dihydro-3-nitropyridines [50, 51]. In the case of unsubstituted XIIa (R = H) in the reaction with methyl acrylate one can isolate a monoaddition product that undergoes thermal cyclization to 2-amino-3-nitro-4,5-dihydro-6-pyridone [50].



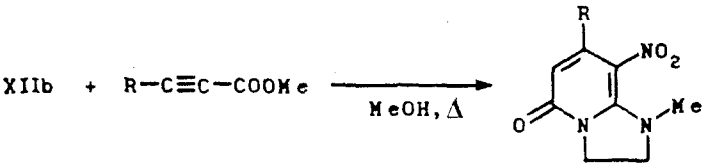
Less active unsaturated ketones and aldehydes react similarly with nitro ketene aminals XIIa, but in the presence of catalytic amounts of acids (see Table 1) [50].



In contrast to the preceding examples, 2-amino-3-nitro-1,4-dihydropyridines, which are formed in the reaction of benzylidene ketones with noncyclic nitro ketene aminals, are readily aromatized [52].

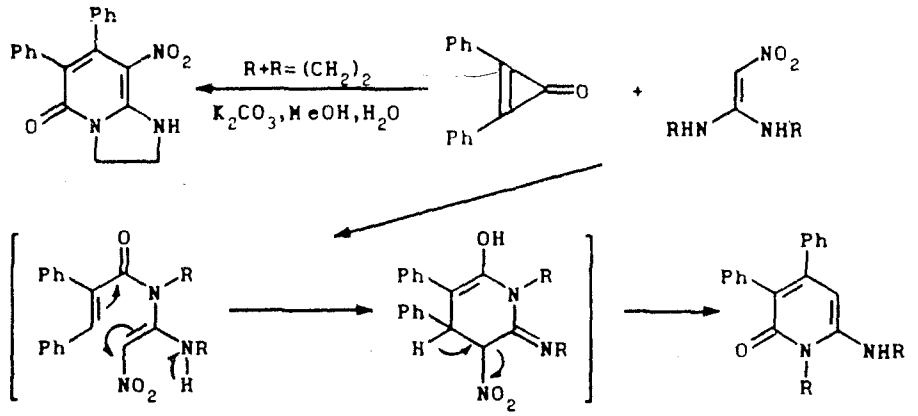


Acetylenic esters react with 2-nitromethyleneimidazolidine (XIIb, R = Me) to give aromatic 3-nitropyridones [51].

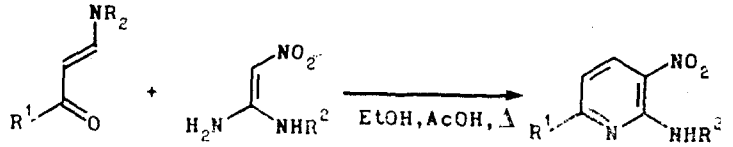


R=H (20h, 62%), R=COOMe (3h, 77%)

In reactions with nitro ketene aminals diphenylcyclopropane behaves like acetylenic esters [53]. 3-Nitro-6-pyridone can be obtained only when R+R = $(CH_2)_2$, while the nitro group is eliminated when R = Ar or R+R = o-phenylene.

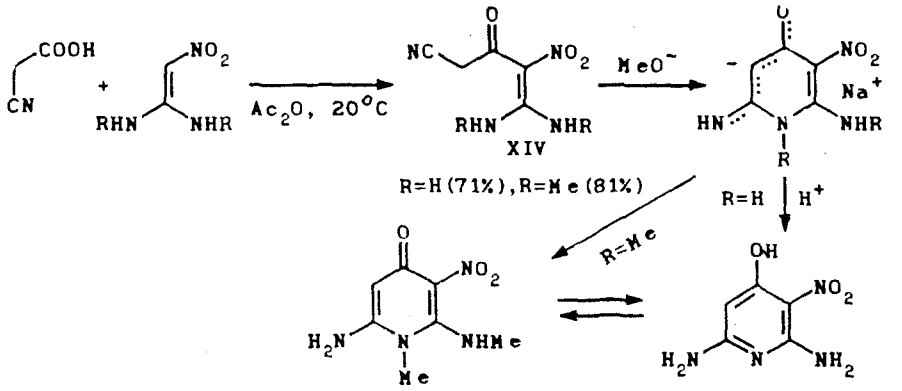


β-Dimethylaminovinyl ketones — the open forms of acetylenic ketones — form the corresponding 6-substituted 2-amino-3-nitropyridines under these conditions [54].

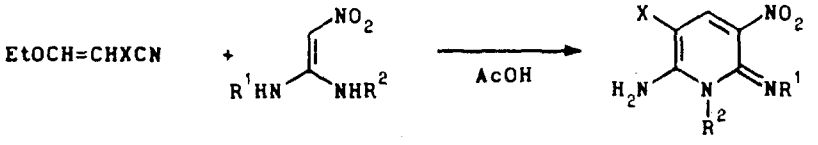


R^1=Me, R^2=Me (73%), $(CH_2)_2Ph$ (62%), $(CH_2)_2CH(OMe)_2$ (58%), CH_2CO_2Et (56%);
R^1=Ph, R^2=CH_2Ph (66%), $(CH_2)_2Ph$ (50%), $(CH_2)_2CH(OMe)_2$ (60%), CH_2CO_2Et (53%)

Cyanoacetic acid reacts as a 1,3-biselectrophile in a stepwise manner; the ketene aminal is initially cyanoacetylated regioselectively in the 2 position, after which the resulting amino nitrile XIV undergo intramolecular cyclization to 2,6-diamino-3-nitro-4-pyridone [55].

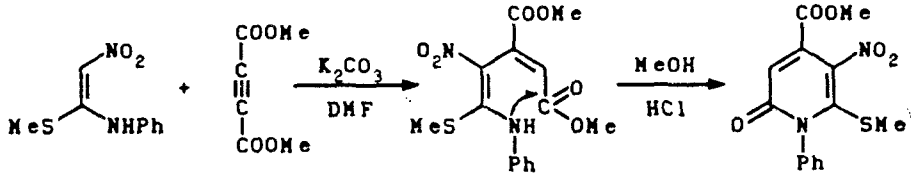


Cyclization at the CN group also occurs in the similar reaction of ethoxymethylenecyanoacetic acid derivatives, and 4-unsubstituted 3-nitro-6-amino-2-pyridone imines are formed [56].

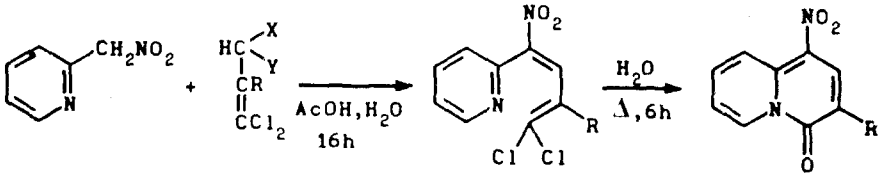


R^1, R^2=Ph, *p*-MeC_6H_4, Et, $(CH_2)_2$; X=CN, CO_2Et

Other biselectrophiles, including dimethyl acetylenedicarboxylate, can also be used in this reaction [57].

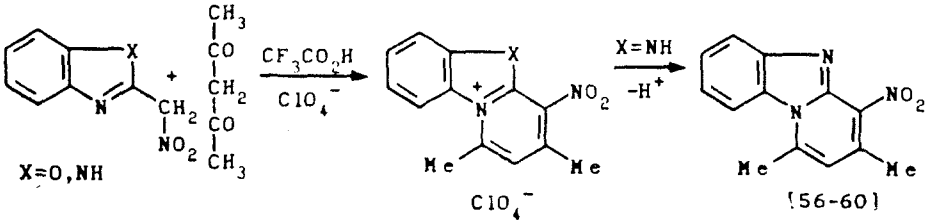


The use of the $-N=C-CH_2NO_2$ fragment, which is a component of α-(nitromethyl)-substituted heterocycles, to construct the nitropyridine fragment leads, due to condensation with β-dicarbonyl compounds or their open forms, to nitropyridines that are annelated with the starting heterocycle in the 1 and 2 positions [56-60].



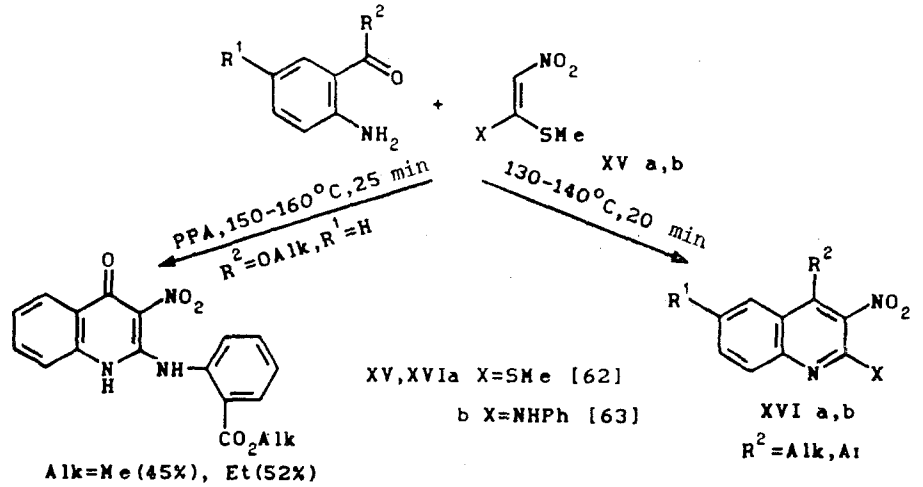
X,Y=O; X=Y=OEt; X=OEt, Y=Cl

R=Et (38%) [56]



[56-60]

It is known that the readily accessible nitro ketene dithioacetals XVa [57], upon reaction with amines, are converted to nitro ketene aminals [61]. When o-acylanilines are used as the amine component, 2-methylmercapto-3-



XVIa R^1=H, R^2=Me (53%), Ph (76%), *p*-MeC_6H_4 (56%); R^1=Cl, R^2=Ph (52%) [62]; XVIб R^1=H, R^2=Me (42%), Ph (73%), *p*-MeC_6H_4 (57%), OH (44%); R^1=Cl, R^2=Ph (46%); R^1=Br, R^2=Ph (65%)

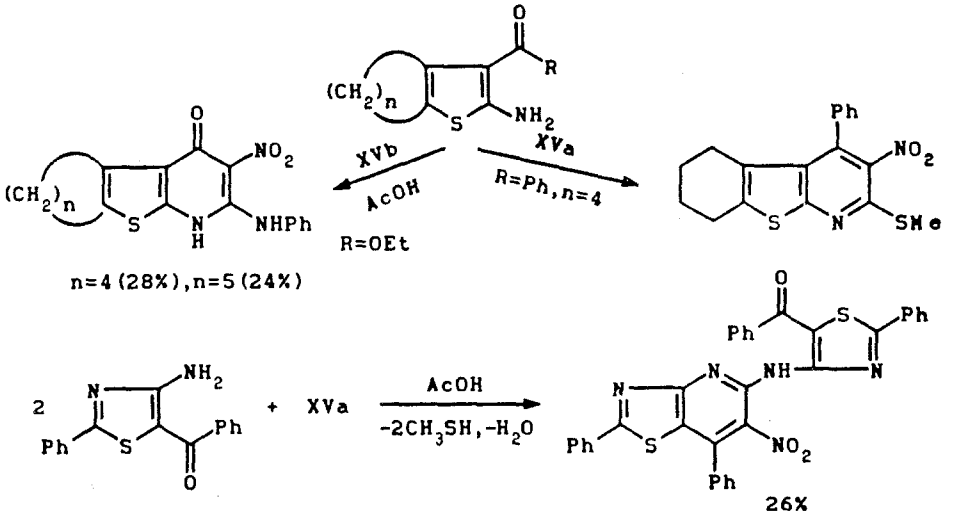
TABLE 2. 3-Nitroquinolines

R^1	R^2	R^3	Yield of quinoline, %			R^1	R^2	R^3	Yield of quinoline, %		
			$ZnCl_2$	PPA	Aniline				$ZnCl_2$	PPA	Aniline
H	H	H	21 [66]	29 [69]	41 [67]	H	MeO	MeO	—	58 [69]	—
H	Me	H	17 [69]	58 [69]	77 [67]	H	NO_2	H	—	0 [70]	0 [69]
H	H	Me			55* [67]	H	H	MeO	—	—	93 [69]
Me	H	H	—	17 [69]	6 [67]						

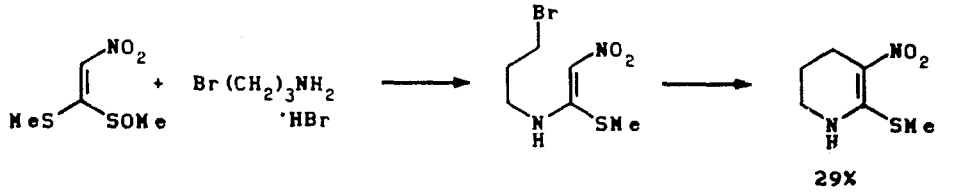
*The yield of a mixture of 5- and 7-methyl-3-nitroquinoline.

nitroquinoline derivatives XVIa are formed during the subsequent acidic cyclization [57, 62]. The condensation of nitro synthones XVa with anthranilic acids gives 2-arylamino-3-nitro-4-quinolones [57, 63]. Replacement of the nitrodimethylmercaptoethylene component by 1-nitro-2-anilino-2-mercaptoethylene compound XVb leads to 2-arylamino derivatives [57, 63].

Heterocyclic analogs of anthranilic acid behave similarly [57, 62-64].

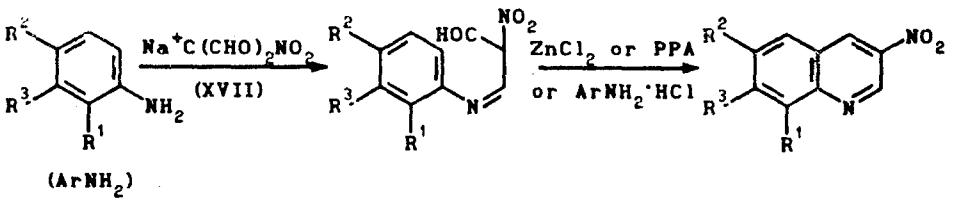


The oxidation of one of the thiomethyl groups of XVa creates a sulfenyl group, which is readily replaced by nucleophiles. Thus N-(3-bromopropyl)thioaminal, which is formed under mild conditions, undergoes cyclization to 1,4,5,6-tetrahydro-3-nitropyridines under the influence of bases [65].



1.2. Formation of the $C_{(4)}$—$C_{(5)}$ Bond

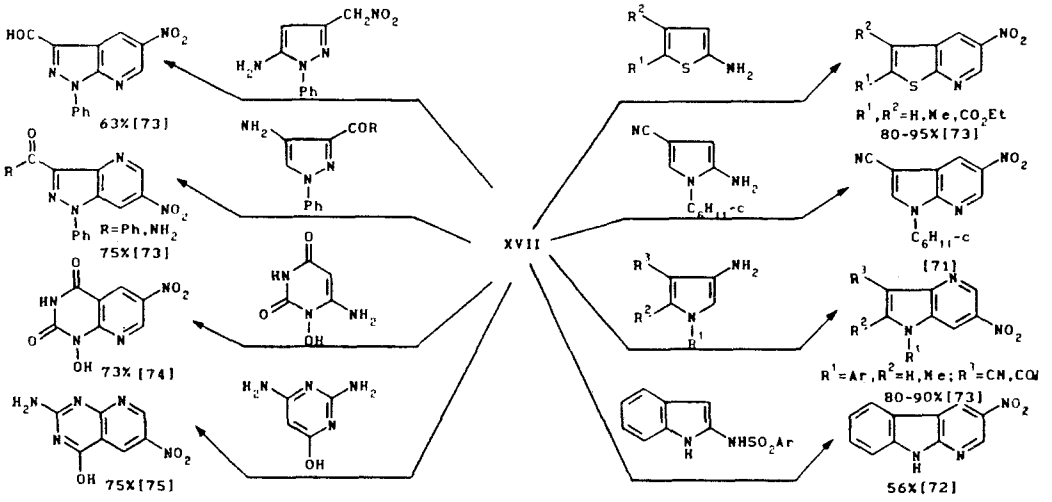
The construction of the 3-nitropyridine skeleton through the formation of a $C_{(4)}$—$C_{(5)}$ bond based on the use of three-carbon nitro synthones (nitromalonic dialdehyde and its derivatives, α-nitro-β-dicarbonyl or α,β-unsaturated carbonyl compounds). Various compounds that contain an explicit or potential enamine grouping are used as the two-carbon fragment necessary for the formation of the pyridine ring.



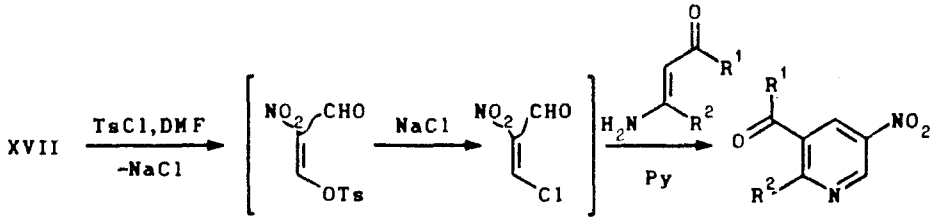
Nitromalonic dialdehyde XVII reacts with anilines to give Schiff bases, which then undergo cyclization to 2,4-unsubstituted 3-nitroquinolines (see Table 2) [66-70].

The use of isomeric naphthylamines in this reaction makes it possible to obtain linear 6,7-benzo- [67] and angular 5,6-benzo-3-nitroquinolines [66].

Diverse heterocyclic amines react with nitro synthone XVII to give heteroannelated 3-nitropyridines [71-75]. The intermediate Schiff bases can be isolated and cyclized by heating in PPA; without isolation of the Schiff bases the reaction is carried out in refluxing acetic acid. The Schiff bases of β-aminothiophenes do not undergo cyclization to 5-nitrothieno[3,2-b]pyridines [73].

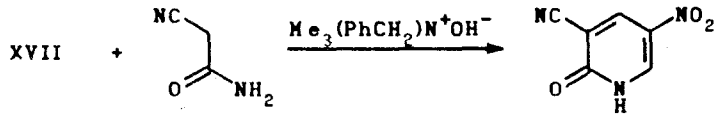


Enamino ketones and enamino esters are also capable of serving as a donor of a two-carbon fragment. In 1953 Fanta first described the synthesis of 3-nitro-5-ethoxycarbonylpyridine from ethyl aminocrotonate and nitro aldehyde XVII [76]; this reaction was previously used only in the quinoline series. Further research showed that Fanta did not use the aminocrotonate but rather the ammonium salt of acetoacetic ester, while the enamine itself forms only traces of the corresponding 3-nitropyridine under these conditions [77]. Hoffman and coworkers [77] found an elegant method for carrying out the reaction with enamino carbonyl compounds involving activation of the nitro synthone by tosylation.



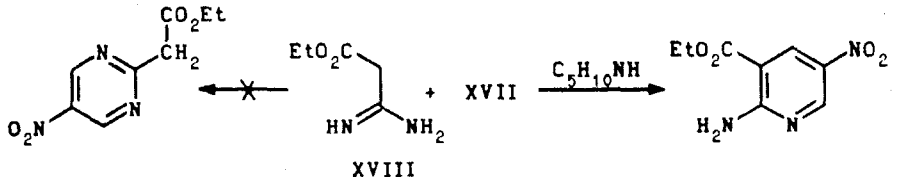
R^1=Me, R^2=H (53%); $R^1+R^2=(CH_2)_3$ (54%), $(CH_2)_2$ (10%); R^1=OEt, R^2=Me (61%); $R^1=R^2$=H (5%)

Cyanoacetamide has been used to obtain 5-nitro-2-pyridone derivatives in the reaction with nitro aldehyde XVII in the presence of Triton B [78-80].



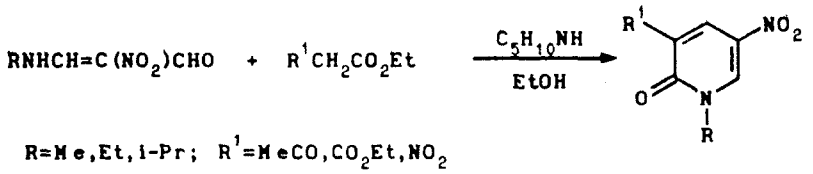
93% [78]

Amidino ester XVIII reacts with nitro aldehyde XVII only as a 1,3-bis-C,N-nucleophile to give exclusively a pyridine ring [81, 82].



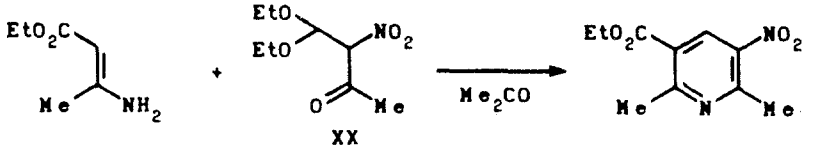
XVIII

The nitrogen atom necessary for the construction of the pyridine ring may also be present in the nitro synthone. Thus nitroaldehyde XVII enamine reacts with CH-acid compounds (for example, malonic and nitro acetic esters, etc.) in the presence of piperidine to give 5-nitro-2-pyridone derivatives [83, 84], while alkyl ketones are inert under these conditions [85].



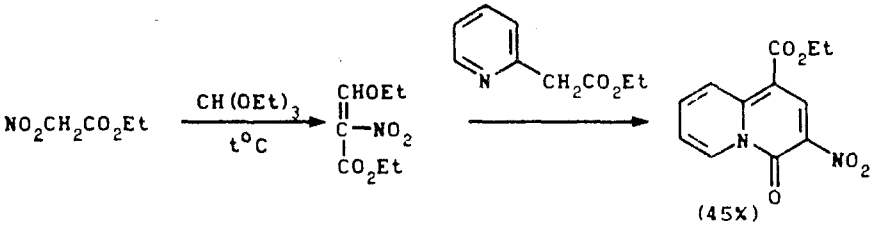
R=Me,Et,i-Pr; R^1=MeCO,CO_2Et,NO_2

A homolog of nitroaldehyde XVII — nitroacetoacetaldehyde diethylacetal (XX) [86] — behaves like it.



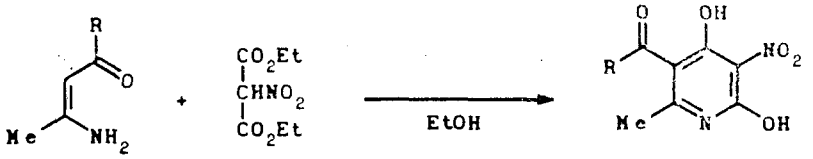
XX

Ethoxymethylenenitroacetic ester — a nitroaldehydo acid derivative — condenses with α-pyridylacetic ester to give a nitroquinazoline derivative [87].



(45%)

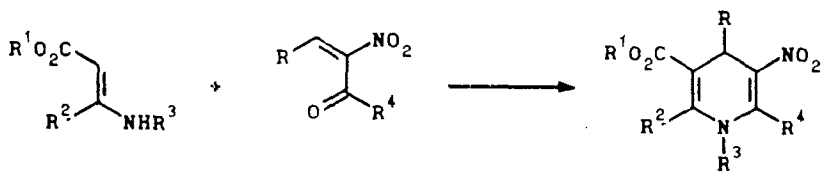
A nitro dicarboxylic acid derivative — nitromalonic ester — reacts with enaminocarbonyl compounds to give the corresponding 3-nitro-2,4-dihydroxypyridines [88].

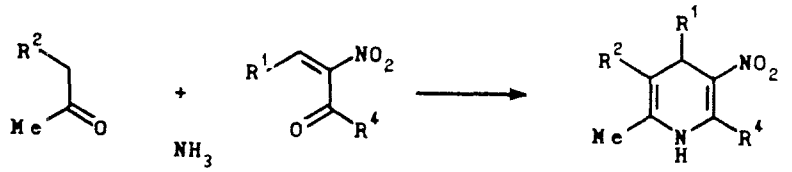


R=Ph(29%),CEt(35%)

Only patent data (see Sec. 1.1 above) have been devoted to the use of α-nitro-α,β-unsaturated ketones in the condensation with ketones and ammonia or aminocrotonates to obtain substituted 1,4-dihydro--3-nitropyridines [34-40, 89-92] (see scheme below).

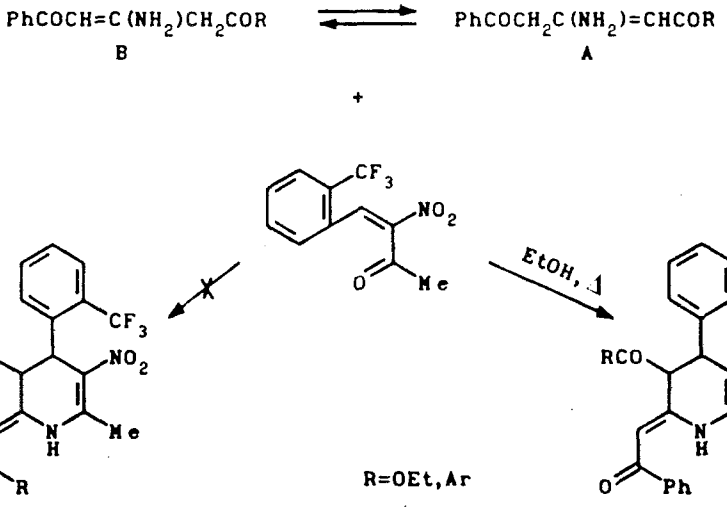
When 1-benzoyl-3-ethoxycarbonylacetone imine, which is capable of undergoing enolization at both CH_2 groups, is used as the donor of a two-carbon fragment, of the two possible enamine forms in the condensation with



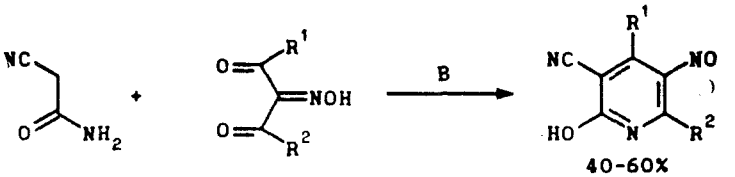


The expansion of the radicals is presented in Sec. 1.3.

substituted 2-nitrochalcones, the A form proves to be more reactive. α-(Benzoylmethylene)tetrahydropyridine is formed in low yield as a result [93].

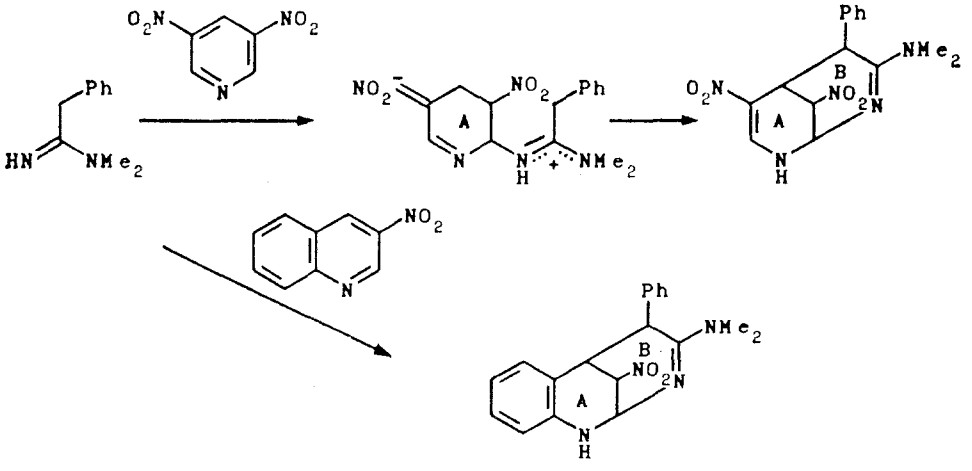


Some of the methods for the construction of a 3-nitropyridine ring examined in this section are also suitable for obtaining 3-nitroso analogs. Thus 3-nitroso-2-pyridinols were obtained in the reaction of cyanoacetamide or cyanoacetamidine and isonitroso β-dicarbonyl compounds [94, 95].



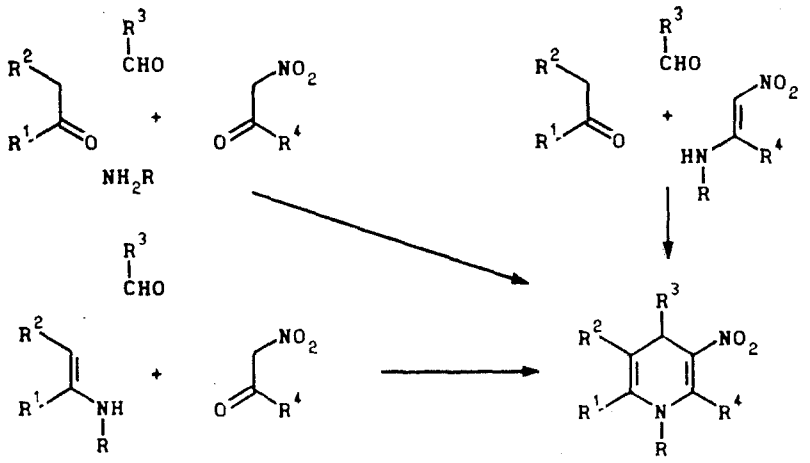
R^1, R^2=Me, OEt, OH, Ph, *p*-ClC_6H_4, *p*-MeC_6H_4

Finally, we may cite a completely unusual variant of the formation of the $C_{(4)}$—$C_{(5)}$ bond. This is a process that involves meta bonding of phenylacetamidine with 3,5-dinitropyridine and 3-nitroquinoline and is accompanied by the formation of a new pyridine ring (B), which also contains a nitro group in the 3 position; other regioisomers were not detected [96].



1.3. Formation of the $C_{(3)}$—$C_{(4)}$ + $C_{(4)}$—$C_{(5)}$ Bonds

The simultaneous formation of $C_{(3)}$—$C_{(4)}$ and $C_{(4)}$—$C_{(5)}$ bonds is observed when a three-component process is used for the construction of 1,4-dihydro-3-nitropyridines [34-40, 89-93, 97-105].

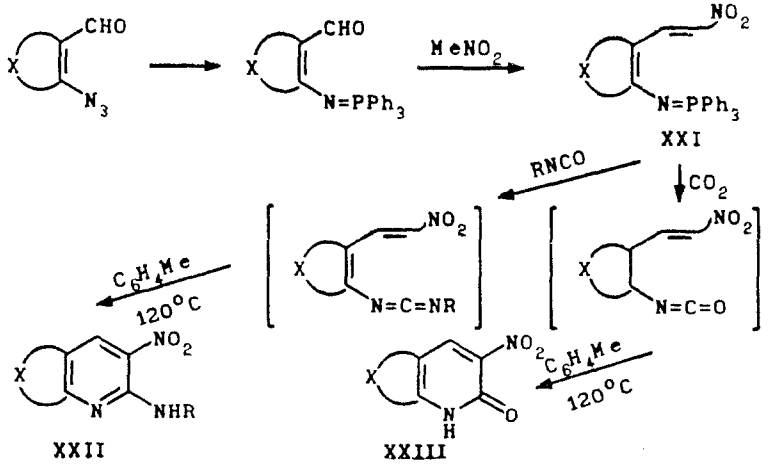


In the overwhelming majority of cases the dihydropyridines are (also see Sections 1.1 and 1.2) 2,6-dimethyl-4-aryl-3-nitro-5-carboxylic acid. However, in some cases they also contain other substituents: $\mathbf{R^4}$ = CN, CH_2-iso-Pr, $CH_2O(CH_2)_2NH_2$, Et [40], Ph, Alk up to C_6, OH-, Hal-, and Ph-substituted [108]; $\mathbf{R^3}$ = Alk up to C_8 (including cyclic) [91, 107, 108], α- [107] and β-naphthyl [98], 2-pyrrolyl, 5-imidazolyl [40], thienyl [91, 107, 108], furyl [107], benzoxazolyl, benzoxadiazolyl [100, 106, 107], 2- [106], 3- [38, 98, 106], and 4-pyridyl [98], 2- and 4-alkoxy-6-pyridyl [40], quinolyl, isoquinolyl [107], pyrimidyl [107]; $\mathbf{R^2}$ = NO_2 [38, 98, 99], CN [99], Cl [98], Ph [91, 107], p-XC_6H_4 (X = Cn, Cl) [86], $CH_2O(CH_2)_2NR_2$, $COCH_2NR_2$ [40]; $\mathbf{R^1}$ = Et [40, 91, 98, 107], Pr [98, 107], CH_2Ph [91, 98], 1-phenyl-2-cyclopropyl [39], CH_2OH [40], NH_2 [98], CN [40]; **R** = Me [98].

The use of only the aldehyde and the nitro ketone gives a mixture of symmetrical 1,4-dihydro-3,5-dinitropyridines [97-108]; hexamethylenetetramine (urotropin) is used as the source of formaldehyde in this reaction [109].

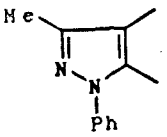
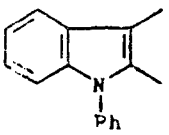
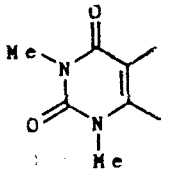
1.4. Formation of the $C_{(2)}$—$C_{(3)}$ Bond

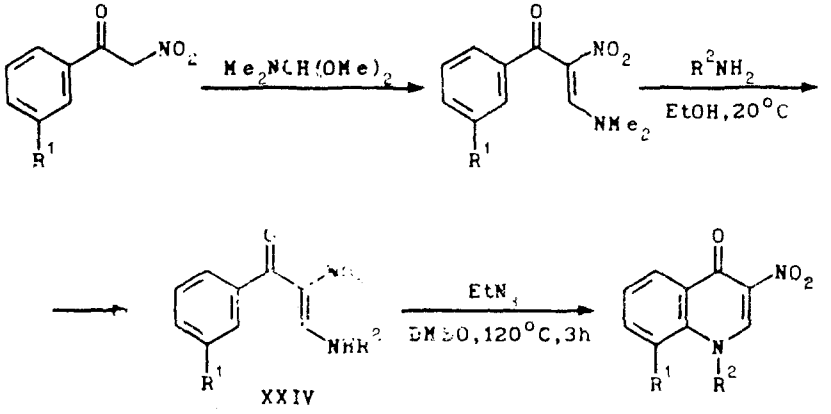
The strategy of the most interesting of the methods involving the formation of a $C_{(2)}$—$C_{(3)}$ bond is the combination of the aza-Wittig reaction of iminophosphoranes XXI with heterocumulenes (isocyanates, CO_2) with thermal 6π-electrocyclization [109-111]. The yields of the heteroannelated 3-nitropyridines are given in Table 3.



Another variant of the formation of the $C_{(2)}$—$C_{(3)}$ bond is its formation in a step involving the intermediate when an enamino grouping is introduced into the α position of α-nitroacetophenone by means of DMF acetal with subsequent transamination and cyclization of the resulting nitro enamino aryl ketone XXIV to 3-nitro-4-quinolones [112].

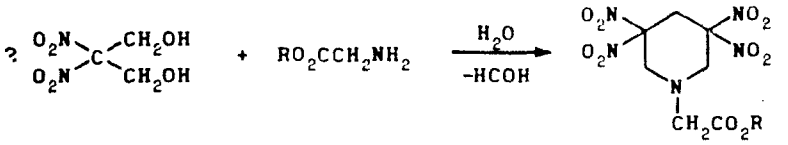
TABLE 3. Heteroannelated 3-Nitro-2-pyridones

Compound	R	Yield,%	Lit. Cited
XXIIa 	Me	60	[109]
	CH_2—CH=CH_2	50	[109]
	Ph	55	[109]
	p-MeC_6H_4	56	[109]
	p-$MeOC_6H_4$	60	[109]
XXIII a		55	[109]
XXII b 	Et	80	[110]
	Ph	80	[110]
	p-ClC_6H_4	93	[110]
	p-MeC_6H_4	79	[110]
	p-$MeOC_6H_4$	97	[110]
XXIII b		96	[110]
XXII c 	Ph	67	[111]
	p-ClC_6H_4	76	[111]
	m-ClC_6H_4	73	[111]
	p-FC_6H_4	60	[111]
	p-MeC_6H_4	70	[111]
	p-$MeOC_6H_4$	68	[111]
	m-$MeOC_6H_4$	71	[111]

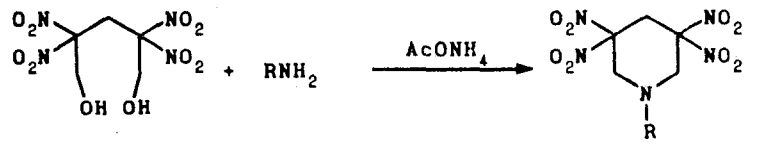


R^1=H, R^2=CH_2Ph (55%); R^1=Cl, R^2=*p*-ClC_6H_4 (41%), *p*-MeC_6H_4 (60%); CH_2Ph (40%), C_4H_9 (90%)

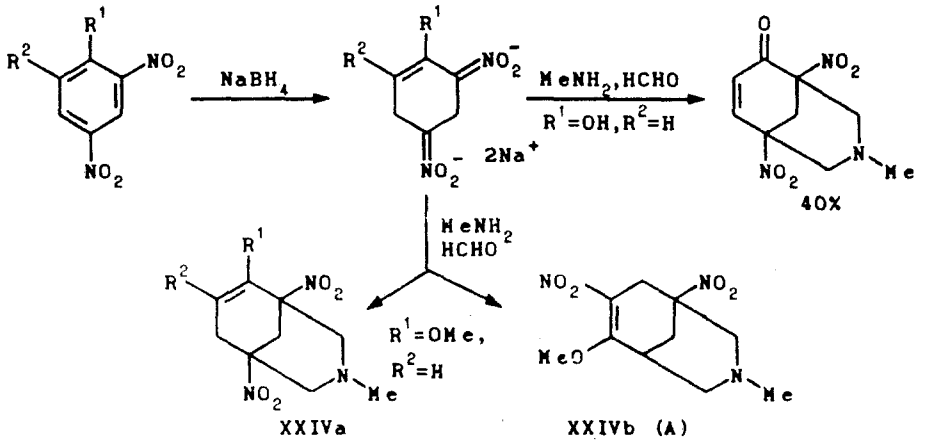
The formation of two identical $C_{(\alpha)}$—$C_{(\beta)}$ bonds of 3,5-dinitropyridines in the Mannich reaction of the 1,3-dinitropropane fragment with two molecules of formaldehyde and a molecule of RNH_2 [113-117] may also serve as an example.



R=H(52%),Et(20%) [113]

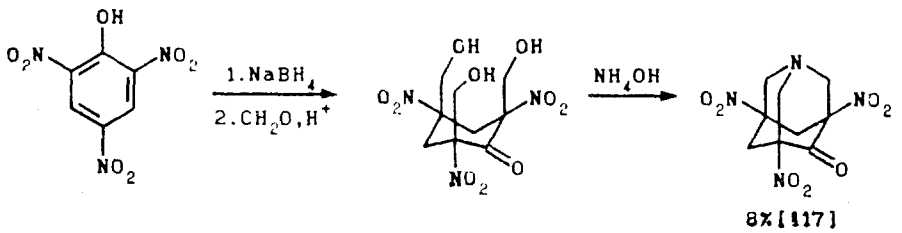


R=H(54%), TMS(17%), CF_3(47%), $(NO_2)_2CHCH_2$(63%), [114]
$NO_2(Me)N(CH_2)_2$ (68%)



XXIVa XXIVb (A)

XXIVa R^2=H,R^1=H(80%),Me(58%), Cl(44%), $PhCH=CH_2$(52%)[115]
R^1=OMe,R^2=H(27% +8% A), R^1=H,R^2=OMe(64%)[116]



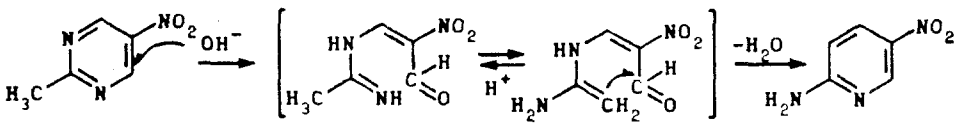
8%[117]

2. TRANSFORMATIONS OF HETEROCYCLES

2.1. Transformation of 5-Nitropyrimidine

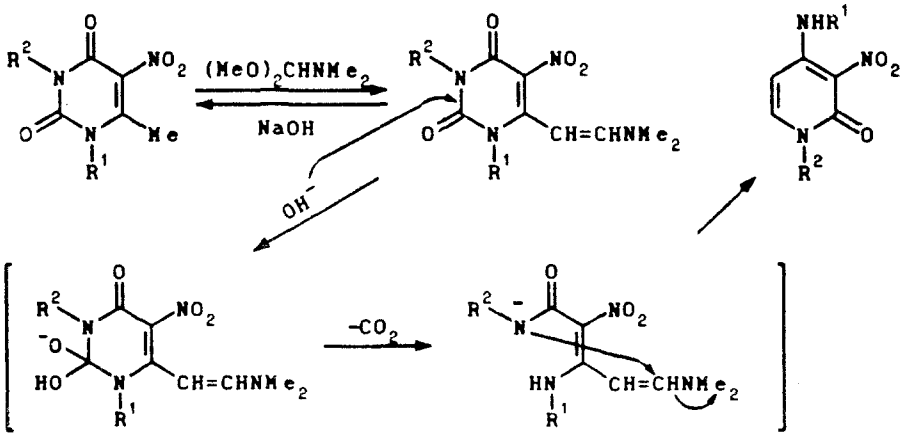
The π-deficient ring of 5-nitropyrimidine and its derivatives is readily opened by the action of C-, N-, or O-nucleophiles, thereby undergoing further diverse transformations, many of which lead to 3-nitropyridine systems.

For example, 2-amino-5-nitropyridine was isolated in 8% yield when 2-methyl-5-nitropyrimidine was heated in aqueous alkali [118].



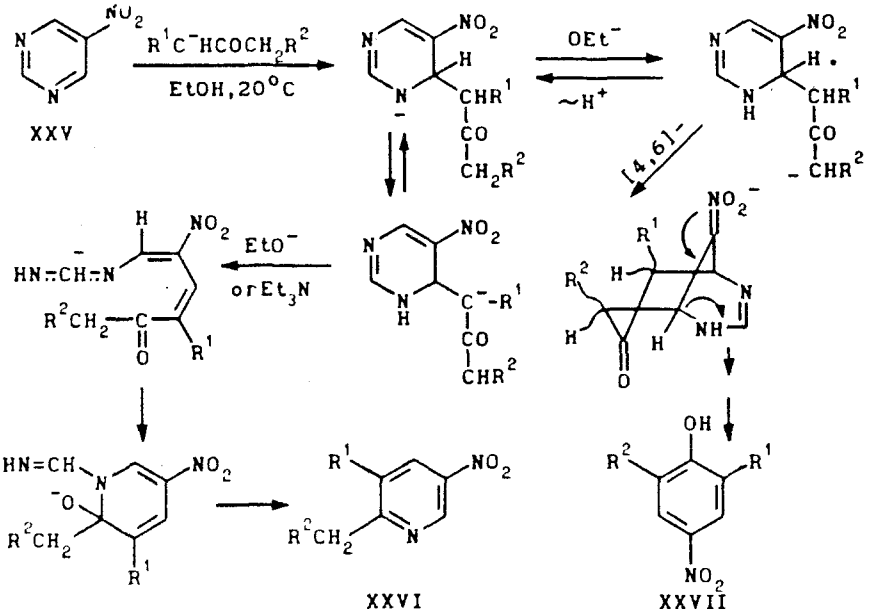
This process takes place via an ANRORC mechanism with initial attack by the nucleophile at the most electron-deficient 4 position of the ring with the subsequent formation of a new pyridine ring with the participation of the methyl group in the 2 position.

The recyclization of 5-nitro-6-(2-dimethylaminovinyl)uracil leads to 4-amino-3-nitro-2-pyridone [119]. Initial attack by the hydroxide ion in this case takes place at the 2 position, and ring opening is accompanied by decarboxylation.



R^1=Me, R^2=H (26%), Me (62%), p-$NO_2C_6H_4$ (21%)

In the case of initial attack by the OH^- group at the 4 position, after decarboxylation, 4-nitromethylene-2-pyrimidone is formed additionally.



The transformation of 5-nitropyrimidine (XXV) under the influence of C-nucleophiles also proceeds via a mechanism similar to the ANRORC mechanism (the formation of σ complexes with ketones was not detected by NMR spectroscopy). A two-carbon fragment of the reactant participates in the construction of 3-nitropyridine XXVI,

TABLE 4. Transformation of 5-Nitropyrimidine by Ketones Action

R^1	R^2	Base	Ketone, moles	Reaction time, h	Yield, %	
					XXVI	XXVII
H	H	NEt_3	1,3	24	33	
Me	Me	NEt_3	1,3	24	30	
Ph	Ph	NEt_3	1,3	24	—	40
Ph	Ph	NEt_3	2,2	15	10	11
MeCO	H	NEt_3	2,2	48	18	
H	H	EtOK	1,3	20	—	10
Me	Me	EtOK	1,3	20	—	48
Ph	Ph	EtOK	1,3	3	—	65
MeCO	H	EtOK	1,3	5	23	

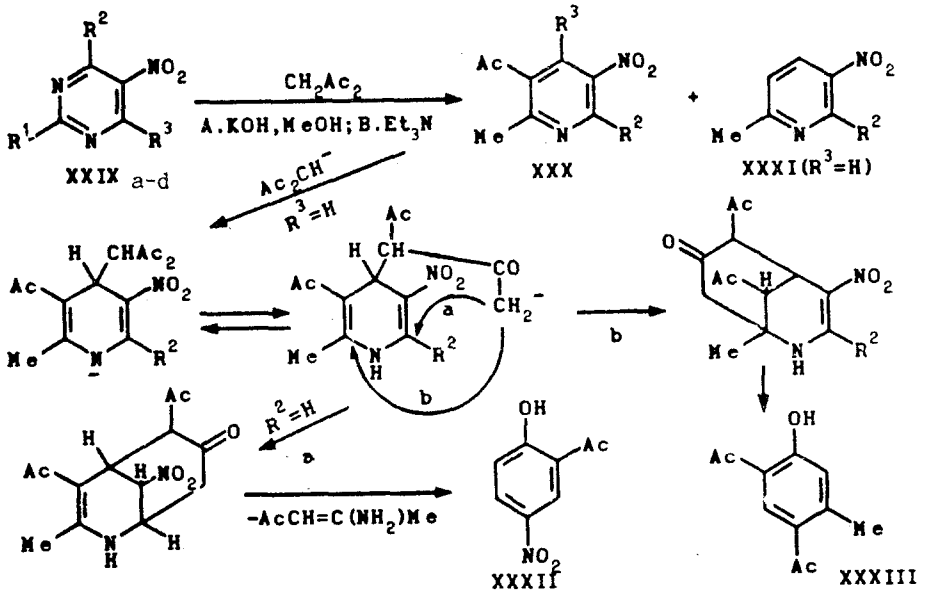
TABLE 5. Conditions for the Conversion of 5-Nitropyrimidines

Starting compound	Reaction conditions		Yield, %			
	Method	Time, h	XXX	XXXI	XXXII	XXXIII
XXIX a	A	5	—	4	3	4
	B	4	23	—	4	4
XXIX b	A	8	—	—	13	—
XXIX b	B	4	—	—	34	—
XXIX c	A	3	6	4	—	4
	B	4	—	—	—	8
XXIX d	A		does not recyclize			
	B	5	—	—	—	7
XXX[a]	B	10	—	—	9	8

*In a mixture with 14% 2-hydroxy-5-nitropyrimidine [123].

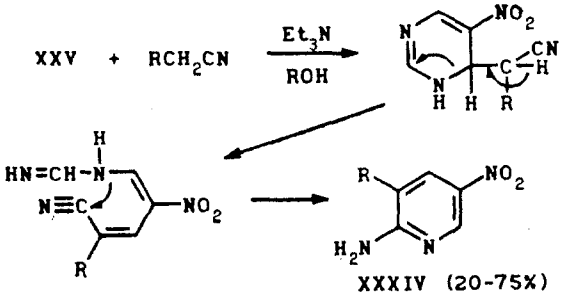
and the pyrimidine ring is the donor of a triatomic nitro-containing fragment, i.e., replacement of the $N_{(1)}$—$C_{(2)}$ fragment of the pyrimidine ring by the two-carbon fragment of the nucleophile formally occurs. The reaction pathway is determined by the structure of the ketone and the character of the base and substituents in the pyrimidine ring (see Table 4) [120].

For unsubstituted nitropyrimidine XXV (in contrast to the data in [120]) it has been shown that an increase in the reaction temperature accelerates the reaction and complicates it; the use of alcoholic alkali in place of the alkoxide evidently leads to deacylation of the intermediate and the formation of 5-unsubstituted 3-nitropyridine XXI (see Table 5) [121].



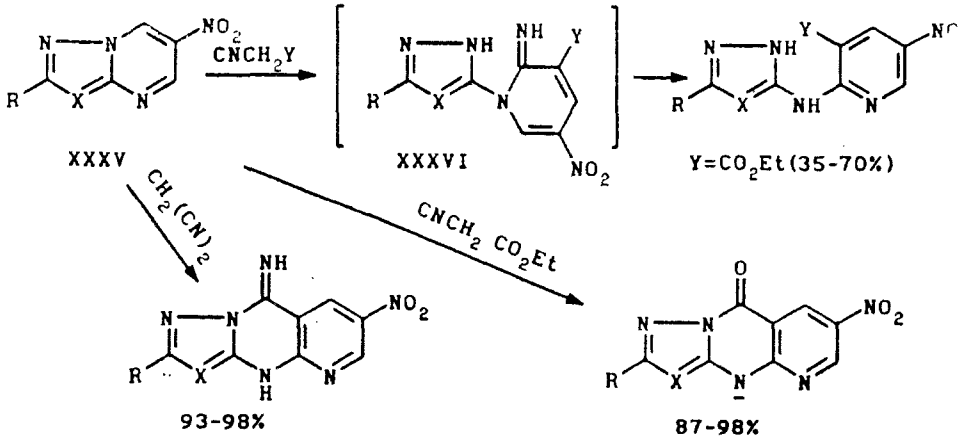
XXIX a $R^1=R^2=R^3=H$ corresponds to XXV); b $R^1=MeO$, $R^2=R^3=H$; c $R^2=MeO$, $R^1=R^3=H$; d $R^3=MeO$, $R^1=R^2=H$

In the case of the reaction with acetylacetone it was shown that, in addition to the formation of phenols XXXII and XXXIII via a meta-bonding mechanism, a secondary process involving transformation of the resulting nitropyridine XXX may also serve as a reason for their development [121, 122].



Acetonitriles are also capable of bringing about the pyrimidine—pyridine transformation of XXV, but only those with acceptor substituents; the CN group participates in the construction of the 3-nitropyridine ring, and this leads to 5-substituted 2-amino-5-nitropyridines XXXIV [123].

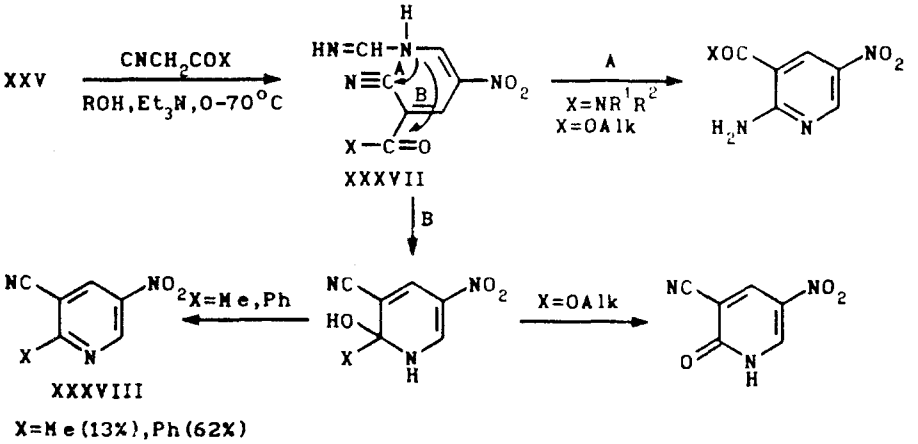
In contrast to noncondensed systems, the transformation of condensed 5-nitropyrimidines (6-nitroazolo[1,5-*a*]pyrimidines) XXXV under the influence of cyanoacetic acid derivatives proceeds without the elimination of the pyrimidine $N_{(1)}$—$C_{(2)}$ fragment as a consequence of the Dimroth rearrangement of the intermediate 1-azolyl-6-imino-3-nitropyridine intermediate XXXVI [124], which leads to azolylamino derivatives of 3-nitropyridine [124-126].



R=H, Me, MeS, CF_3, Cl, NH_2, NMe_2; X=N, C—CO_2Et, C—NO_2

Subsequent cyclization resulting in the formation of a new pyrimidine ring occurs in the presence of a base (Na_2CO_3) or when cyanoacetic ester is replaced by malonodinitrile [124].

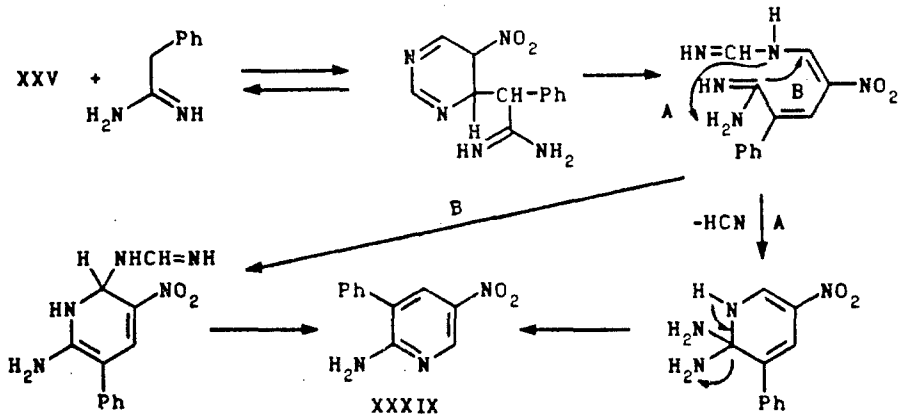
The presence of a carbonyl group in the nitriles creates the possibility of ring formation in intermediate XXXVII both at the cyano and carbonyl groups, depending on the substituents attached to them. Cyanoacetamides (X = NR^1R^2) react only via pathway A, keto nitriles (X = Me, Ph) react only via pathway B (to give 2-substituted 3-cyano-5-nitropyridines XXXVIII), while cyanoacetic esters react via both pathways — at low temperatures cyclization takes place primarily at the carbonyl group, while cylization also begins to occur at the CN group with an increase in the temperature [123].



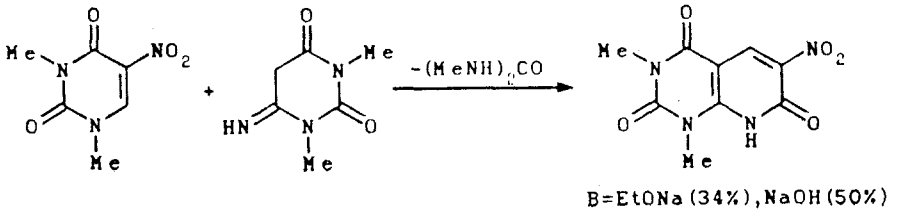
NR^1R^2=pyrrolidine NHCO$_2$EtAlk=Me, Et, *t*-Bu

α-Phenylacetamidine — a polyfunctional reagent that is capable of acting as both a 1,3-N,N- or 1,3-C,N-bisnucleophile and as an electron-donor olefin (in its enediamine form) — reacts with nitropyrimidine XXV to give 2-amino-5-nitro-3-phenylpyridine (XXXIX() [127, 128] (see scheme below)

An experiment with the labeled ^{15}N-phenylacetamidine showed that the transformation proceeds equally via two pathways — with replacement of the $N_{(1)}$—$C_{(2)}$—$N_{(3)}$ (pathway B) or $C_{(2)}$—$N_{(1)}$ (pathway A) fragment of the

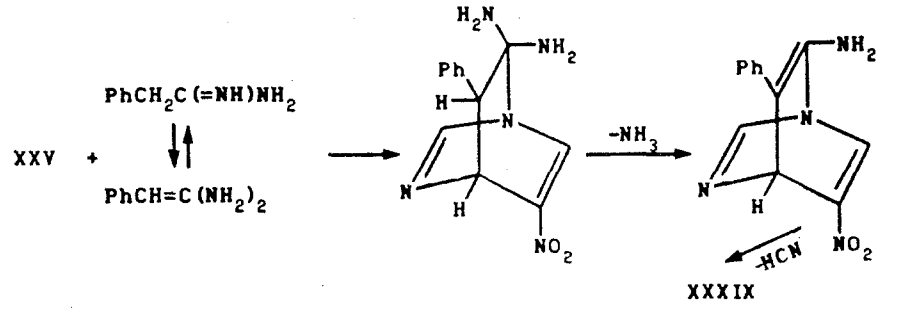


pyrimidine ring by the C—C—N or C—C function, respectively, of the amidine [127].



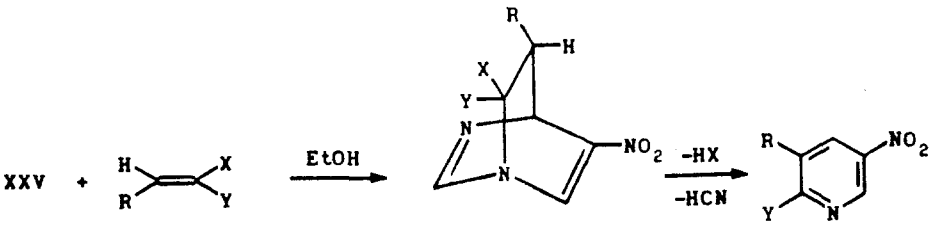
A similar approach was used to obtain a condensed pyrido[2,3-*a*]pyrimidine on the basis of the reaction of 5-nitrouracil with a cyclic amidine — 6-aminouracil [129].

Charushin and van der Plas [127] have also postulated another approach to the reaction pathway of the pyrimidine—pyridine transformation under the influence of amidines — not through 1,3-cycloadducts but rather through 1,4-cycloadducts, i.e., via the Diels—Alder reaction with reversed electronic requirements of the diene system of the nitropyrimidine and the enediamine form of the amidine.



This sort of pathway is confirmed by the formation of 2-morpholino-5-nitropyridine in the reaction of nitropyrimidine XXV with a fixed enediamine form of the amidine — 1,1-dimorpholinoethylene [127].

This assumption is also confirmed brilliantly by a large series of studies of the inter- and intramolecular [4+2]-cycloaddition of the azadiene system of nitropyrimidine XXV and electron-surplus alkenes and alkynes [130-137]. The first example described in the literature was the regioselective transformation of pyrimidine XXV under the influence of ketene N,N- and O,O-acetals and enamines [130].



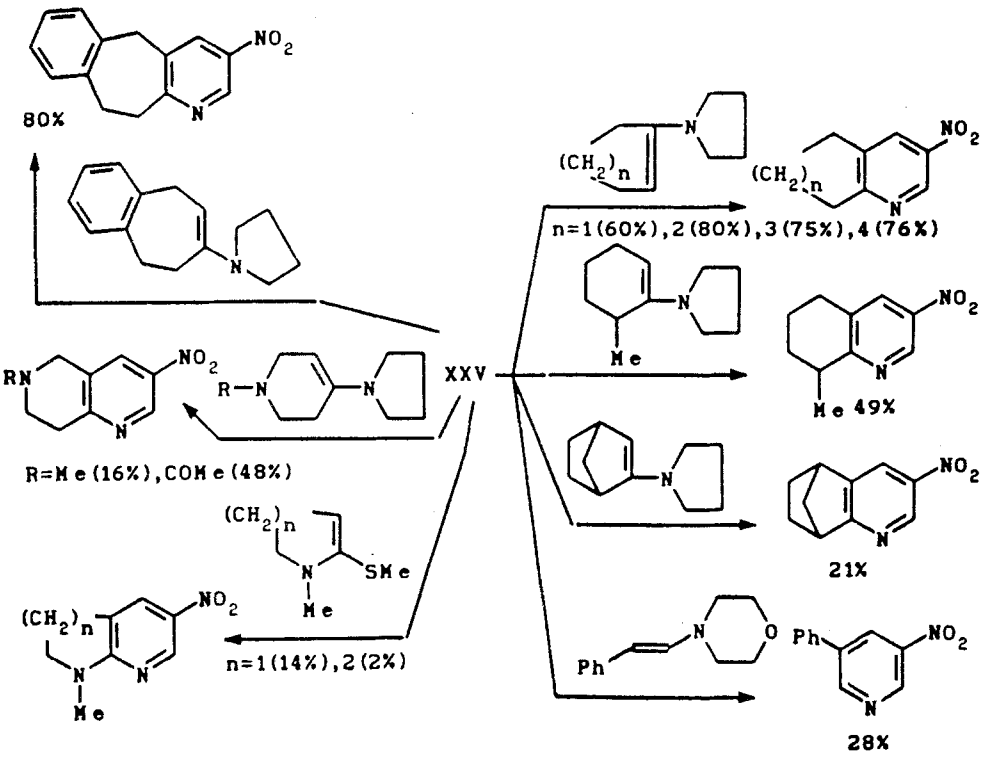
R=H, X=Y= morpholino(49%); R=H, X=Y= piperidino(52%); R=Me, X=Y=OMe (17%); R+Y=$(CH_2)_4$, X= morpholino (80%); R+Y=$(CH_2)_3$, X=pyrrolidino (60%)

TABLE 6. Transformation of 5-Nitropyrimidines

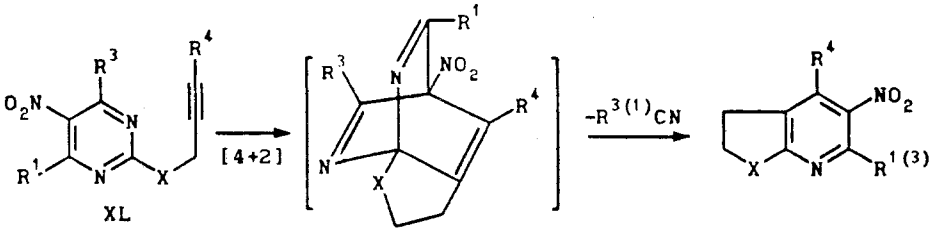
R	$R^{1(2)}$	$R^{2(1)}$	R^3	Yield, %		
				XLI	XLII	XLIII
Me	H	H	H	Traces	50	—
Me	Me	H	H	(R^1=H) 13; (R^1=Me) 2	50	15
Me	MeO	H	H	21	—	38
Me	H	H	Me	50...60	—	—
Me	H	H	MeO			
Me	H	H	Ph			
Me	MeO	MeO	H	52	—	—
Me	MeO	H	MeO	—	—	68
Ph	H	H	H	8	—	44

The experimentally observed orientation of cycloaddition at the 1 and 4 positions of pyrimidine is confirmed by means of the theory of perturbation of the boundary orbitals in the case of the reaction of pyrimidine XXV with 1,1-dimorpholinoethylene [131].

The immense synthetic possibilities of the use of enamines of various ketones as dienophiles were demonstrated in [133].



Pyrimidines that have an ω-alkynyl side chain in the 2 or 5 position undergo a similar intramolecular thermal transformation, leading to heteroannelated 3-nitropyridines [134, 135].

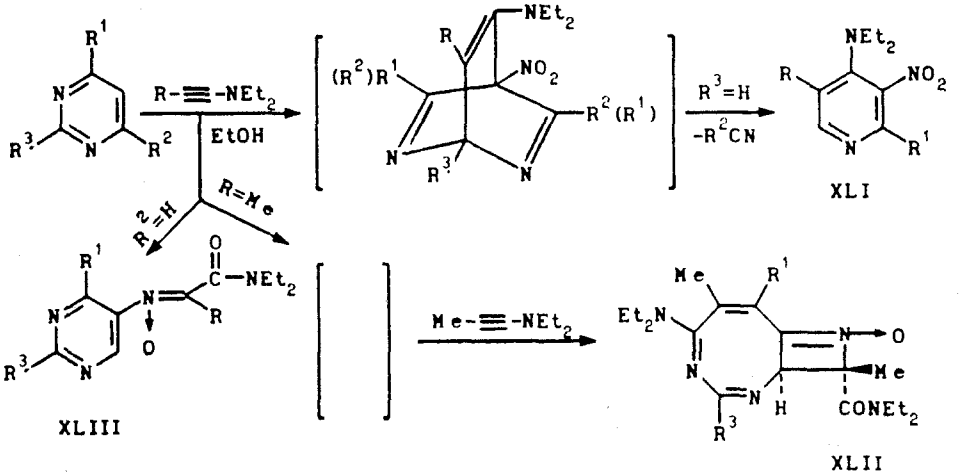


$R^{1(3)}$=H, X=O (55%), S (75%), NAc (87%)

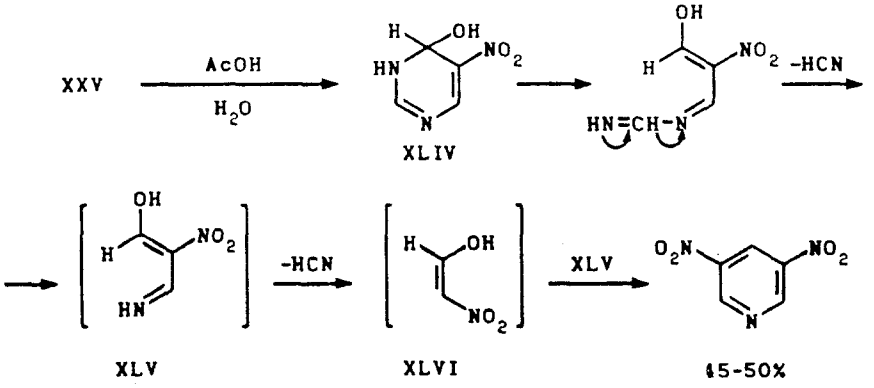
The reactivities increase in the order X = NH < O < S < NCOMe; this is due to the decrease in dating in the π system of pyrimidine [135]. According to this logic, the presence of an aliphatic carbon atom, in place of a heteroatom, as the bonding link between the pyrimidine and the dienophile should increase the ability to undergo the transformation. In fact, in the case of pyrimidines XL [R^1 = R^3 = R^4 = H, X = $C(CN)_2$] the reaction takes place

in only 6 h at 130°C and gives the products in 96% yields [136, 137]. The somewhat lower activity of XL (X = CH_2, 210°C, 30 min, 58% yield) as compared with the activity of XL [X = $C(CN)_2$] cannot be explained only by electronic factors. Frissen and coworkers [137] ascribe this appreciable change in the rate to the "gem" effect [138], which is manifested in a decrease in internal angle $C_{(2)}—C_{(\alpha)}—C_{(\beta)}$ and drawing together, as a consequence of this, of the reaction centers. The need to increase the temperature to 210°C to achieve the same effect with an increase in the length of the chain [X = $C(CN)_2CH_2$] serves as a confirmation of this [137].

In contrast to enamines, the cycloaddition of ynamines to 5-nitropyrimidines proceeds ambiguously. Although, according to PMR data, a stable (in solution) 2,5-bicyclic adduct is formed in the reaction of N,N-diethylamino-1-propyne with unsubstituted nitropyrimidine XXV, virtually no conversion of it to the corresponding 3-nitropyridine XLI occurs [130]. In this case, just as for other 4,6-unsubstituted 5-nitropyrimidines, an adduct with two propyne molecules — azetodiazocene XLII [139] — is isolated from the reaction. Marcelis and and van der Plas [133] were able to direct the reaction (completely or partially) to favor the formation of the corresponding 3-nitropyridines XLI only by varying the structure of the reaction components (see Table 6).

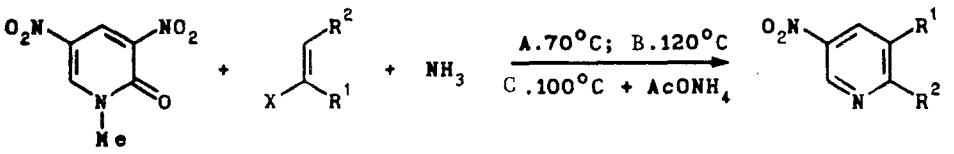


An unusual transformation leading to the production of 3,5-dinitropyridine was observed when nitropyrimidine XXV was heated in aqueous acetic acid [140], although there are several opinions regarding the stability of the pyrimidine ring in acidic media. The process evidently takes place through a step involving covalent hydration to give 1,6-dihydro-6-hydroxy-5-nitropyrimidine (XLIV) and cleavage of the C—C bond in this intermediate to give two fragments, viz., nitromalonic dialdehyde imine (XLV) and nitroacetaldehyde (XLVI), the recombination of which also leads to 3,5-dinitropyridine [140].



2.2. Transformation of Other Heterocycles

In Sec. 1.2 we demonstrated that the reaction of nitromalonic dialdehyde with a mixture of ammonia and a methylene carbonyl compound (or its enamine) leads to 2,4-unsubstituted 3-nitropyridines. It was established that 1-methyl-3,5-dinitro-2-pyridone is the activated masked equivalent of nitromalonic dialdehyde. The reaction of this pyridone with the most diverse methylene carbonyl compounds (or their enamines) with ammonia is a preparative method for the synthesis of a large number of 2,4-unsubstituted 3-nitropyridines that are difficult to obtain by other methods [141].



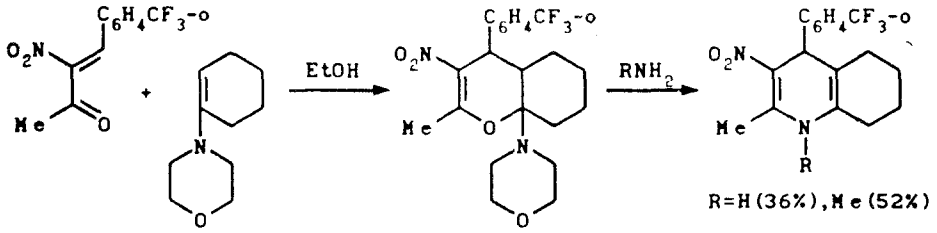
X=OH or N-morpholino

R¹	R²	Yield, % A	Yield, % B	Yield, % C	R¹	R²	Yield, % A	Yield, % B	R¹	R²	Yield, % B
H	Me	0	0	18	*i*-Pr	H	56	21	2-Pyridyl	H	72
H	Et	Traces	—	32	*t*-Bu	H	Traces	69	2-Furyl	H	62
H	Pr	0		32	Ph	H	49	81	2-Thienyl	H	50
H	*i*-Pr			52			90*		*p*-YC_6H_4**	H	44
$(CH_2)_5$		27; 37*	14		Ph	Me	10	37	MeO		64
					Ph	Ph	Traces	33; 66*	Me		73
$(CH_2)_6$		83; 90*	28						CN		30
									NO_2		27

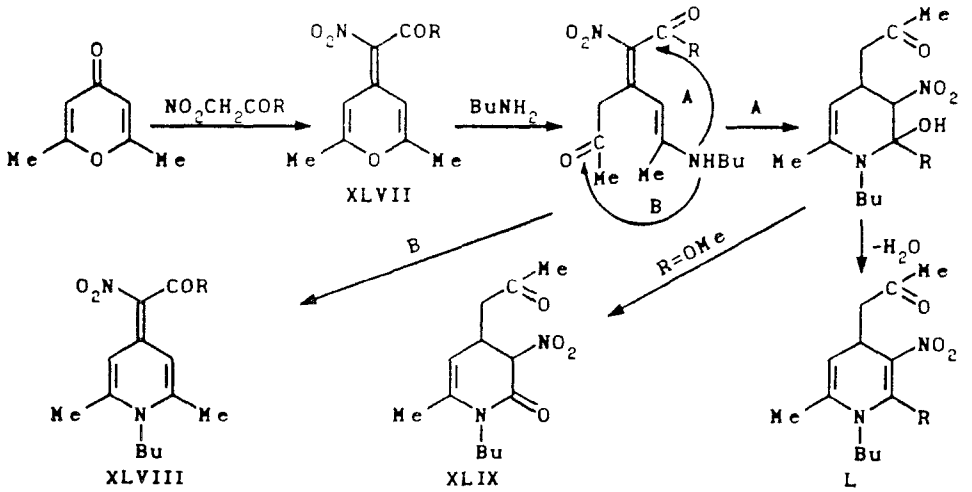
*Yields with the morpholine enamine of the ketone.

**Y = NH_2.

The reaction of arylidene nitro ketones with enamines gives chromene intermediates, which are converted to 1,4-dihydropyridine derivatives by the action of ammonia or primary amines [142, 143].

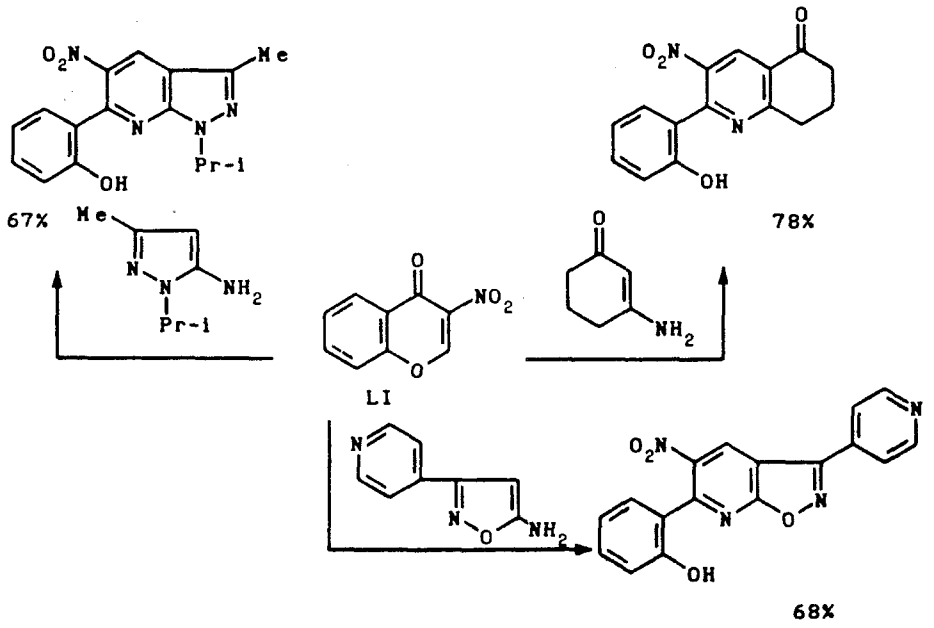


A nitromethyl derivative (XLVII) of γ-pyrone undergoes recyclization via an ANRORC mechanism to give a 3-nitropyridine derivative under the influence of butylamine [144].

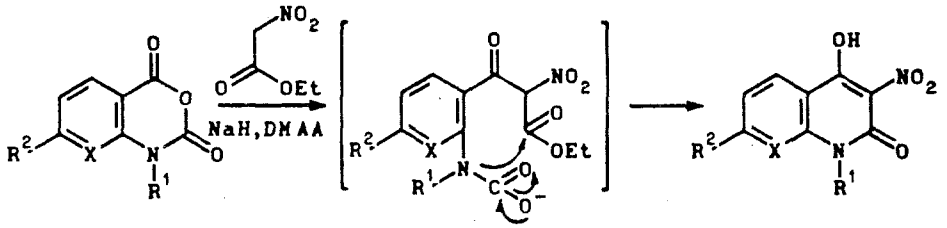


R=Me, XLVIII (34%), L (30%); R=OMe, XLIX (34%)

Under the influence of cyclic enamines 3-nitrochromones LI form 2-(o-hydroxyphenyl)-3-nitropyridine derivatives [145].

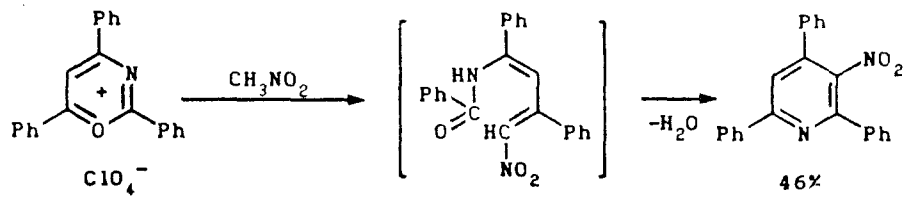


2H-3,1-Benzoxazin-2,4(1H)-dione (isatoic anhydride) is readily cleaved by the action of the nitroacetic ester carbanion with subsequent cyclization to the corresponding quinozolones [146, 147]. The similar reaction of 3-azaisatoic anhydride leads to 3-nitro-1,8-naphthyridine derivatives [148-150].

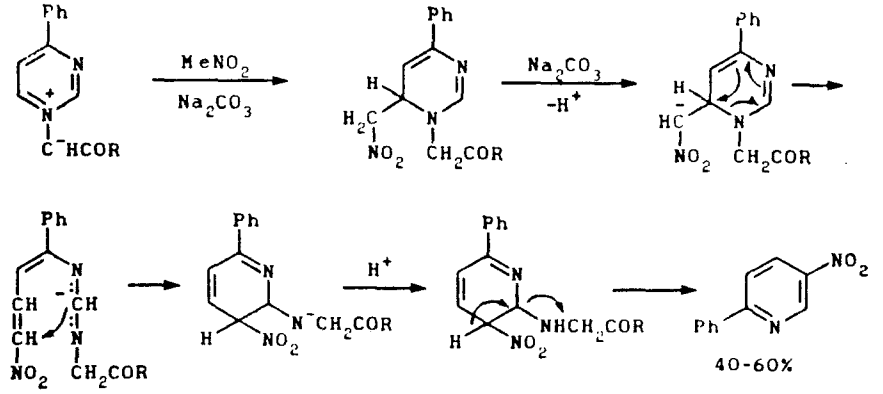


X=CH, R^1=Me, R^2=H (42%); X=N, R^1=Me, R^2=H (22%); X=N, R^1=$CH_2CH{=}CH_2$, R^2=H (29%); X=N, R^1=R^2=Me (26%)

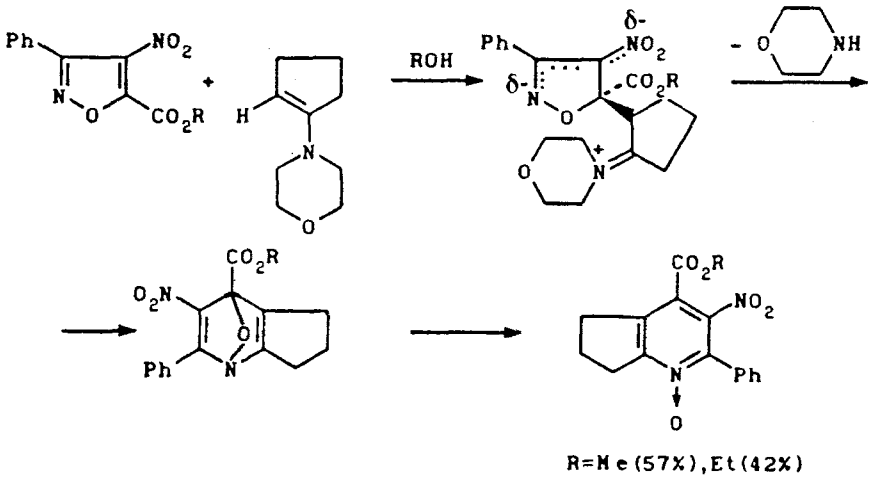
This reaction can be formally regarded as replacement of the ring oxygen atom in the meta position relative to the nitrogen atom by a C—NO_2 fragment. Similar substitution in the triphenyloxazinium series leads to triphenyl-3-nitropyridine [151].



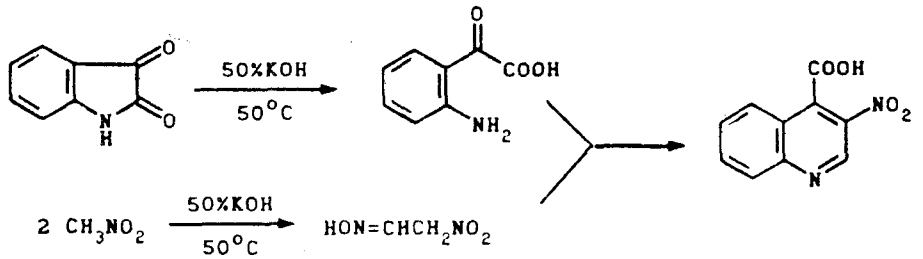
The quaternized nitrogen atom, as, for example, in a pyrimidine ylid, can also be replaced [152].



Nesi and coworkers [153] classify the conversion of 4-nitro-3-phenyloxazole-5-carboxylates to N-oxides of the corresponding 2-phenyl-3-nitropyridines by the action of enamines as a stepwise ionic [4+2]-cycloaddition (azadiene synthesis) [153].



Isatin reacts with nitromethane in an alkaline medium to give 3-nitrocinchoninic acid [154], which is a consequence of the transformation of both reactants under the reaction conditions: isatin is hydrolyzed to an o-amino keto acid, while nitromethane undergoes condensation to give nitroacetaldehyde oxime (metazonic acid). The final result is the well-known synthesis of quinolines from o-acylanilines and metazonic acid (see Section 1.1).



Thus the existence of such variously devised methods for the synthesis of compounds with a 3-nitropyridine skeleton in the literature makes the most diverse compounds of this series accessible and makes it possible in each individual case to select the most effective method on the basis of the most accessible starting material.

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