NITROAZINES. METHODS OF SYNTHESIS (REVIEW)

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Published data on methods for the production of six-membered nitrogen heterocycles containing a nitrogroup are classified systematically.

Six-membered nitrogen heterocycles containing a nitro group in the ring form a considerable class of organic compounds. They find use in various branches of technology, medicine, and agriculture. Individual sections in reviews on electrophilic substitution in azines [1, 2] and on the nitration of nitrogen heterocycles [3] have been devoted to the chemistry of nitroazines. In 1979 a review was published on the synthesis of heterocyclic compounds from aliphatic nitro derivatives [4], in which there is a small section concerning azines. Brief data on the subject can also be found in monographs and reviews devoted to pyrimidines, pyridazines, or pyrazines [5-8]. However, there are no systematic data in the literature.

A whole series of methods for the production of the nitro derivatives of azines are based on attainments in the chemistry of nitroarenes. This concerned primarily electrophilic nitration and also the oxidation of amino and nitroso compounds and, to a lesser degree, substitution of halogen and other ready leaving groups of the nitrite ion. However, it should be noted that the direct adoption of methods from the arsenal of the chemistry of aromatic compounds has substantial limitations. The aza group, which is susceptible to protonation and specific solvation, greatly deactivates the aromatic system to electrophilic attack, has a marked effect on the affinity of the nitroso or amino group to the oxidizing agent and on the basicity of the amino group, and also makes its very existence problematical on account of amino–imine tautomerism. All this cannot fail to affect the realization of the reactions. The production of the nitro derivatives of azines by the closure of rings from aliphatic nitro synthons, compared with the analogs not containing nitro groups, also has its peculiarities associated with the increased CH acidity, the ambident character of the nitroalkanes, their possible existence in the aci form, etc.

In the present review an attempt is made to summarize and classify published data on the methods for the introduction of a nitro group into the azine ring.

ELECTROPHILIC NITRATION

Electrophilic nitration in the series of six-membered heteroaromatic compounds is far from being realized in every case. In comparison with aromatic hydrocarbons the reaction takes place under much more drastic conditions; the replacement of one =CH– group by =N– leads to a decrease of 10^6 times in the nitration rate [1]. In addition, protonation of the azine is possible when the reaction is realized in an acidic medium, and this retards the reaction by 10^{12}–10^{18} times. The accumulation of aza groups deactivates the molecules even more. The successful nitration of diazines, for example, is only possible with the presence of strong electron-donating substituents in the molecule.

Nitropyridines. Unsubstituted pyridine is nitrated under very drastic conditions and gives low yields [9]. Donating substituents facilitate the entry of the nitro group into the azine ring, but the effect of the substituents cannot be predicted unambiguously. A systematic investigation of the kinetics of the nitration of pyridine derivatives [10-16] has shown that basic compounds ($pK_a > 1$) containing electron-donating groups react in the protonated form while weakly basic compounds ($pK_a < -2.5$) react in the form of a free base. Thus, for example, 2,6-dichloropyridine (I, $pK_a - 2.86$), unlike the unsubstituted compound, reacts even at 100°C [16]. In the case of 2,6- and 3,5-dimethoxypyridines (II, III), which react in the protonated form (pK_a 1.0 and 4.44), the introduction of the first nitro group

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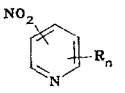
TABLE 1. Nitropyridines

	Nitration conditions	Yield, %	Reference
3-NO_2	HNO_3, 20% oleum, 300°	4,5	9
2-CH_3-3-NO_2	KNO_3, 18% oleum, 180°	3	18, 19
2,4-$(CH_3)_2$-3-NO_2	KNO_3, 30% oleum, 100°	50	19, 20
2,6-$(CH_3)_2$-3-NO_2	KNO_3, 20% oleum, 100°	66	18, 20
2,4,6-$(CH_3)_3$-3-NO_2	KNO_3, 18% oleum, 100°	90	18, 19
2,6-Cl_2-3-NO_2	HNO_3, H_2SO_4, 100°	48	10
	HNO_3, 65% oleum, 100°	72	11
2-NH_2-3-NO_2	HNO_3, H_2SO_4, 40°	20	21, 22
2-NH_2-5-NO_2	HNO_3, H_2SO_4, 40°	63	21, 23
2-NH_2-3-CH_3-5-NO_2	HNO_3, H_2SO_4, 40°	90	21, 24
4-NH_2-3-NO_2	HNO_3, H_2SO_4, 160°	—	25
2-NHPyc-5-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 20°	90	26, 27
2-N$(CH_3)_2$-5-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 0°	51	28
2-N$(CH_3)_2$-3,5-$(NO_2)_2$	HNO_3 (*d* 1,5), H_2SO_4, 20°	81	28
3-N$(CH_3)_2$-2-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 0°	8	28
4-N$(CH_3)_2$-3-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 20°	81	28—30
2-OH-3-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 80°	50	31
2-OH-3,5-$(NO_2)_2$	HNO_3 (*d* 1,5), H_2SO_4, 100°	51	32
2-OH-6-CH_3-3-NO_2	HNO_3 (*d* 1,5), CH_3COOH, 100°	—	33
2-OCH_3-5-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 100°	—	33
2,6-$(OCH_3)_2$-3-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 0°	76	10
2,6-$(OCH_3)_2$-3,5-$(NO_2)_2$	HNO_3 (*d* 1,5), H_2SO_4, 50°	68	34
3-OH-2-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 0°	—	13, 35
3-OH-2,6-$(CH_3)_2$-4-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 20°	80	36, 37
3-OCH_3-2-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 80°	44	38, 39
3-OC_2H_5-2-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 60°	80	38, 39
3-OCH_3-2,6-$(NO_2)_2$	HNO_3 (*d* 1,5), H_2SO_4, 170°	—	40
3,5-$(OCH_3)_2$-2-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 0°	84	10
3,5-$(OC_3)_2$-2,6-$(NO_2)_2$	HNO_3 (*d* 1,5), H_2SO_4, 40°	30	10
4-OH-3-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 0°	31	41, 42
2,4-$(OH)_2$-3-NO_2	HNO_3 (*d* 1,4), 100°	87	43, 44
4,6-$(OH)_2$-5-NO_2	HNO_3 (33%), 20°	48	40

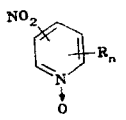
reduces the basicity, and the mononitro compound reacts further in the form of the base, which favors the production of the dinitro derivatives (Table 1).

Thus, on the one hand, successful nitration requires the presence of donating substituents in the molecule and, on the other, the increase in basicity due to this reduces their reactivity. However, in spite of this, a large number of nitropyridines have been obtained by electrophilic nitration; for example, about 100 compounds are given in the patent [17] alone. Examples which make it possible to assess the potentialities of the method for the protection of nitropyridines are given in Table 1.

Alkylpyridines are nitrated more readily than unsubstituted pyridine, and the yield increases greatly with increase in the number of methyl groups [18-20]. Comparison of the reaction rates of 1,2,4,6-tetramethylpyridinum and collidine makes it possible to conclude that the latter reacts in the protonated form. A strong electron donor (the amino group) facilitates electrophilic attack at position 3 even more [21-30]. The nitration of primary amines takes placed in two stages; the nitroaminopyridine is formed initially and then rearranges to the C-nitro derivative [21-24]. Here, whereas 2-nitroaminopyridine rearranges at 40°C with the formation of the 3- and 5-nitro isomers in a ratio of 8:1, 4-nitroaminopyridine requires heating to 160°C. For alkoxy- and hydroxypyridines the direction of the reaction is determined by the ortho-para-directing effect of the substituents [45, 46]. The nitration of 3-hydroxypyridine takes place exclusively at position 2, and the hydroxypyridine reacts in the protonated form [13]. Depending on the conditions, 3-alkoxypyridines form 2-nitro and 2,6-dinitro derivatives [38-40].

Interesting results were obtained with 2-substituted 3-hydroxypyridines, in which substitution takes place not only at position 6 but also at position 4, and the formation of the 4-isomer predominates [12, 33, 37]. In contrast to the 3-isomers, selectivity in attack at positions 3 and 5 is not observed in 2-hydroxypyridines. The direction of the reaction depends largely on the concentration of the reagents and on the activity of the medium; the 3-nitro derivatives are formed preferentially at higher temperatures, larger concentrations of the substrate, and in comparatively dilute sulfuric acid [13].

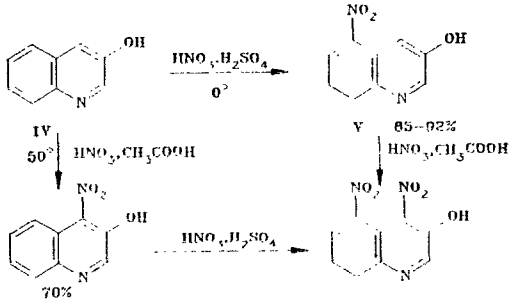
TABLE 2. Nitropyridine 1-Oxides

	Nitration conditions	Yield, %	Reference
4-NO_2	KNO_3, H_2SO_4, 100°	94	1
2-CH_3-4-NO_2	HNO_3, H_2SO_4, 100°	—	1
3-CH_3-4-NO_2	HNO_3(*d* 1,5), H_2SO_4, 50°	60	50
3,5-$(CH_3)_2$-4-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 60°	46	50
2-Cl-4-NO_2	HNO_3, H_2SO_4, 100°	35	49, 51
2-Br-4-NO_2	HNO_3, H_2SO_4, 100°	68	52
3-Br-4-NO_2	HNO_3, H_2SO_4, 130°	50	57
2-OCH_3-4-NO_2	HNO_3, H_2SO_4, 75°	55	57
3-OCH_3-4-NO_2	HNO_3, H_2SO_4, 75°	70—75	58
2-OH-5-NO_2	HNO_3, CH_3COOH, 0°	67	58
2-OH-3,5-$(NO_2)_2$	HNO_3, CH_3COOH, 40°	—	59
3-OH-2-NO_2	HNO_3, H_2SO_4, 15°	60	60
4-OH-3,5-$(NO_2)_2$	HNO_3, CH_3COOH, 100°	80	58
3,5-$(OCH_3)_2$-2-NO_2	HNO_3, H_2SO_4, 0°	—	53
3,5-$(OC_2H_5)_2$-2-NO_2	HNO_3, H_2SO_4, 0°	100	54
2-$N(CH_3)_2$-5-NO_2	HNO_3, H_2SO_4, 0°	22	28
4-$N(CH_3)_2$-3-NO_2	HNO_3, H_2SO_4, 0°	27	28

The nitration of 4-hydroxypyridines takes place under much more drastic conditions [47, 48]. The decrease in the reactivity is clearly due to their preferential existence in the pyridone form. The reaction rates of 2-, 3-, and 4-hydroxypyridines and 1,2,4,6-tetramethylpyridinium were similar, and this indicates preliminary protonation of the substrate [10, 12, 13].

The presence of the N → O group in the pyridine molecule changes the orientation and facilitates electrophilic substitution. Pyridine N-oxide and its alkyl and halogen derivatives are nitrated smoothly at position 4 [49-52]. The directing effect of the N → O group is stronger than that of the alkoxyl and weaker than that of the hydroxyl group. This corresponds to the formation of the 4-nitro derivatives when the alkoxypyridine N-oxides are used and the 2- or 3,5-nitro compounds in the case of hydroxypyridine N-oxides (Table 2). In the presence of two alkoxyl groups, however, the nitro group enters at position 2 [53, 54]. Investigation of the kinetics of this reaction showed that with substitution at position 4 the substrate reacts in the form of the free base while in other cases it reacts in the protonated form [55, 56].

Annellation of the pyridine ring leads to the appearance of additional electrophilic centers. During the nitration of quinoline and 3-hydroxyquinoline there are two types of orientation, depending on the reaction conditions. Treatment of quinoline with concentrated nitric and sulfuric acids gives a mixture of almost equal amounts of the 5- and 8-nitro isomers, while the 5-nitro derivative (V) is mainly formed from 3-hydroxyquinoline (IV) [61-63]. In the reaction with 3-hydroxyquinoline in glacial acetic acid the nitro group enters at position 4 [63]. Under analogous conditions quinoline and 4-quinoline are also nitrated in the pyridine ring [64-66]. Such orientation can be explained by the fact that the substrate is protonated in the first case and not in the second.

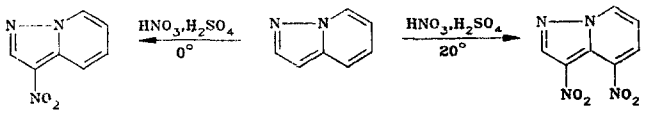


3-Nitro-4-hydroxyisoquinoline was obtained similarly from 4-hydroxyisoquinoline [67].

The few examples among heteroannellated pyridines mainly concern azolopyridines. The production of 3,6-dinitro-5-hydroxy-1H-pyrazolo[3,4-b]pyridine with a yield of 73% [68],

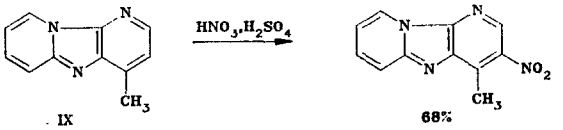
4-hydroxy-7-nitro-1H-imidazo[4,5-c]pyridine [69], and 3-methyl-6-nitroimidazo[4,5-b]pyridine (yields 91 and 50%) [70] under fairly drastic conditions (heating to 100-150°C in a nitrating mixture) has been described.

The nitration of azolopyridines with a bridging nitrogen atom, which is not an "azine" nitrogen and hardly deactivates the molecule at all, takes place much more readily. Calculations of the electron density by the CNDO/2 method for pyrazolo[1,5-a]pyridine (VI) [71, 72] show that the size of the charge at positions 3 and 4 of the molecule of (VI) is close to that for the para-carbon atom of phenol both for the conjugate acid and for the case. The nitration of compound (VI) by a nitrating mixture at 0°C gives 3-nitropyrazolopyridine (VII), while nitration at 20°C gives the dinitro derivative (VIII) [71].



VII 80% VI VIII 53%

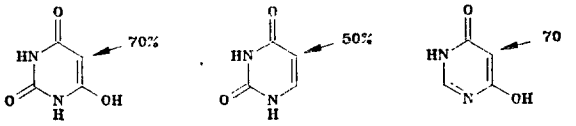
2-Carbozy-4-nitroimidazo[1,2-a]pyridines were obtained under analogous conditions [73]. The nitration of 4-methyldipyrido[1,2-a:3,2-d]imidazole (IX) in the pyridine ring is evidently explained by the fact that in this case the bridging nitrogen atom, which deactivates the rings attached to it, is primarily protonated [74].



IX 68%

Nitropyrimidines. Diazines are more inert than pyridine and especially benzene in electrophilic substitution reactions. The reactivity of unsubstituted pyrimidine is so low that activating electron-donating groups must be present in the molecule for successful nitration (Table 3). When treated with concentrated nitric acid, barbituric acid (X) gives 5-nitrobarbituric (dilituric) acid with a yield of 70% [75]. Uracil (XI) only reacts with boiling nitric acid, giving 5-nitrouracil [76, 77]; 4,6-dihydroxypyrimidine (XII) is nitrated under milder conditions, i.e., in acetic acid at 20°C. Such a difference is due to the state of the tautomeric equilibrium. Uracil is present mainly in the diketo form, and 4,6-dihydroxypyrimidine has one hydroxy and one oxo group [5].

Investigation of the kinetics of the nitration of uracil and N-methyluracils has shown that these compounds react in the unprotonated dioxo form [78].

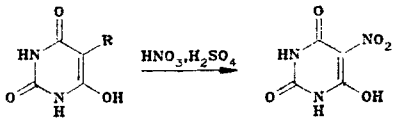


X XI XII

With the presence of amino, alkylamino, alkylthio, or alkoxy groups in the pyrimidine molecule in addition to the hydroxy group nitration with a mixture of nitric and sulfuric acids at 50-60°C gives the corresponding 5-nitro derivatives. 2,4-Diaminopyrimidine [79] and 4,6-diaminopyrimidine [80] are nitrated at position 5 through the intermediate nitroamino derivatives, while monoaminopyrimidines only give the N-nitro compounds, the rearrangement of which into the C-nitro derivatives is not observed [80].

Under drastic conditions it is possible to introduce the nitro group into pyrimidine in the presence of only one activating group. The corresponding 5-nitro derivatives were obtained from 2-hydroxypyrimidine [81] and 4-hydroxypyrimidine [82].

ipso-Nitration has been described in the pyrimidine series. Thus, 5-nitrobarbituric acid can be obtained from the acid (XIII) [83] and 5-mercaptobarbituric [84], 5-nitrosobarbituric (XV) [85], 5-isothioureidobarbituric (XVI) [86], and 5-carbamoylbarbituric (XVII) [87] acids.

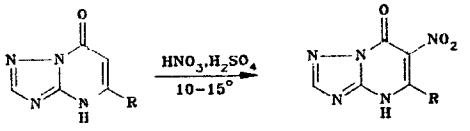


XIII–XVII

XIII R= 2,4,6-Trihydroxy-5-pyrimidinyl; XIV R=SH; XV R=NO; XVI R=SC(=NH)NH$_2$; XVII R=CONH$_2$

The data given in Table 3 make it possible to determine which derivatives can be obtained by nitration.

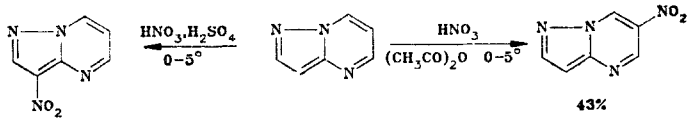
The nitration of heteroannellated pyrimidines depends both on the presence of donating substituents in the substrate and on the reaction conditions. In reaction with a nitrating mixture the structural analog of uracil 7-oxo-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine (XVIII) gives the nitro compound (XIX), while the nitration of 1,2,4-triazolo[1,5-a]pyrimidine cannot be realized [94, 95].



XVIII XIX

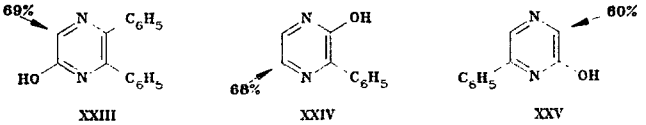
R=H, CH$_3$, OH, NH$_2$

The 3-nitro derivative (XXI) is formed from pyrazolo[1,5-a]pyrimidine (XX) under the same conditions, while 5-nitropyrazolo[1,5-a]pyrimidine (XXII) is formed in a mixture of nitric acid and acetic anhydride [96]. Such a difference in direction is due to the form of the compound which takes part in the reaction. In the first case it is the conjugate acid, and in the second it is the free base.



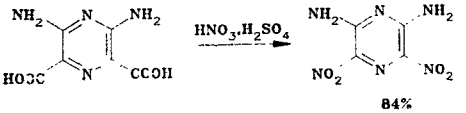
XXI XX 43% XXII

Nitropyrazines. Unlike pyrimidine, in the pyrazine and pyridazine molecules the electronegative effects of the nitrogen atoms situated at the para and ortho positions are unconcerted, and their resultant action is weakened, but here too successful electrophilic substitution requires the assistance of activating group. In arylpyrazines the reaction only takes place in the benzene ring [97], but activation of the pyrazine ring by a hydroxy group leads to the corresponding nitropyrazines (XXIII–XXV), and the hydroxy group has an ortho- and para-directing effect [97-99].



XXIII XXIV XXV

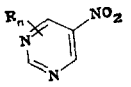
An example of the decarboxylating nitration of 2,6-diaminodicarboxypyrazine is given in the patent [100].



84%

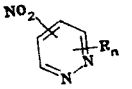
Nitropyridazines. Like other diazines, pyrdiazine is surprisingly stable to nitration [101], and nitration can only be realized when the pyridazine ring is strongly activated by

TABLE 3. 5-Nitropyrimidines*

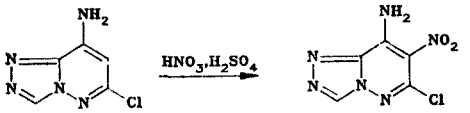
	Nitration conditions	Yield, %	Reference
2,4,6-$(OH)_3$	HNO_3 (*d* 1,5)	70	74
2,4-$(OH)_2$	HNO_3, 100°	50	76, 77
4,6-$(OH)_2$	HNO_3 (*d* 1,5), CH_3COOH, 20°	70	5
2-NH_2-4-OH	HNO_3 (*d* 1,5), CH_3COOH, 25°	50	77
2-OH-4-$NHCH_3$	HNO_3 (*d* 1,5), H_2SO_4, 50°	50	85
2-OH-4-NHC_2H_5	HNO_3 (*d* 1,5), H_2SO_4, 40°	47	88
2-OH-4-NHC_4H_9	HNO_3 (*d* 1,5), H_2SO_4, 50°	60	89
4-OH-6-$NHCH_3$	HNO_3 (*d* 1,5), H_2SO_4, 45°	80	90
4,6-$(NH_2)_2$-6-Cl	HNO_3 (*d* 1,5), H_2SO_4, 40°	85	79
2-CH_3-4,6-$(OH)_2$	HNO_3 (*d* 1,5), CH_3COOH, 20°	85	79
2-C_4H_9-4,6-$(OH)_2$	HNO_3, H_2SO_4, 40—50°	50	79
2,4-$(OC_2H_5)_2$	HNO_3 (*d* 1,5), H_2SO_4, 100°	60	89, 92
2,4-$(OCH_3)_2$-6-CH_3	HNO_3 (*d* 1,5), H_2SO_4, 80°	95	93
2,4-$(OC_2H_5)_2$-6-CH_3	HNO_3 (*d* 1,5), H_2SO_4, 80°	30	93
2-OH	KNO_3, H_2SO_4, 95°	49	81, 82
4-OH	KNO_3, H_2SO_4, 90°	38	82
1-Methyl-2,4-dioxo	HNO_3, H_2SO_4, 20°	80	91
1,3-Dimethyl-2,4-dioxo	HNO_3, H_2SO_4, 20°	80	90, 92

*The possible existence of some of the compounds in the oxo form is not taken into account in the table.

TABLE 4. Nitropyridazines

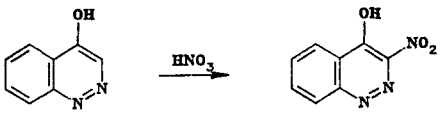
	Nitration conditions	Yield, %	Reference
3,5-$(NH_2)_2$-4-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 55°	88	104
3,6-$(OCH_3)_2$-4-NH_2-5-NO_2	KNO_3, H_2SO_4, 70°	89	102
3,6-$(OC_2H_5)_2$-4-NH_2-5-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 55°	80	105
3-OCH_3-4-NH_2-5-NO_2-6-CH_3	KNO_3, H_2SO_4, 20°	21	103
	HNO_3 (*d* 1,5), H_2SO_4, 55°	64	105
3-OC_2H_5-4-NH_2-5-NO_2-6-CH_3	HNO_3 (*d* 1,5), H_2SO_4, 55°	65	105
3-OCH_3-4-NH_2-5-NO_2-6-Cl	HNO_3 (*d* 1,5), H_2SO_4, 55°	53	105
3-OC_2H_5-4-NH_2-5-NO_2-6-Cl	HNO_3 (*d* 1,5), H_2SO_4, 55°	69	105
3,6-Cl_2-4-NH_2-5-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 55°	70	105
3-Cl-4-NH_2-5-NO_2-6-CH_3	HNO_3 (*d* 1,5), H_2SO_4, 55°	81	105

electron-donating substituents [102-105]. Table 4 gives examples of nitropyridazines obtained by electrophilic nitration. 3,6-Dialkoxy-, 3-alkoxy-6-methyl-, 3-alkoxy-6-chloro-, and 3,6-dichloropyridazines enter into the reaction. 5-Chloro-7-amino-1,2,4-triazolo[4,3-b] pyridazine (XXVI) activated by an amino group reacts at position 6 [106].



XXVI 30%

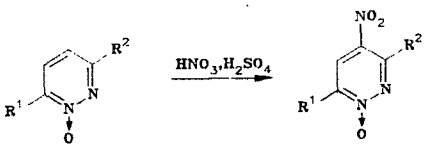
When treated with nitric acid, 4-hydroxycinnoline gives the 3-nitro derivative XXVII [107].



XXVII

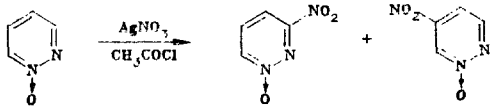
3-Hydroxypyridazine is passive, while the less basic 4,5-dichloro-3-hydroxypyridazine reacts with potassium nitrate and a mixture of sulfuric and nitric acids to form the 6-nitro derivative [108, 109].

As in the case of pyridine, the formation of the N-oxide activates the pyridazine ring to electrophilic interactions. The N-oxide is nitrated at the para position to the N → O group by a mixture of sulfuric and nitric acids at 130–140°C with a yield of 22% [110, 111]. A series of 3,6-disubstituted derivatives of 4-nitropyridazine N-oxide XXVIII were obtained under the same conditions (Table 5) [112-116].



XXVIII

The nitro products are formed with yields of 85–88% during the nitration of 3-alkoxy-5-methyl-6-chloropyridazine 1-N-oxides [117]. If position 4 is occupied, the reaction takes place at position 6 [116]. The 4-mononitro and 4,6-dinitro derivatives were obtained by the action of nitric and sulfuric acids on 3-methoxypyridazine N-oxide [118, 119]. The reaction of pyridazine N-oxide with acyl nitrates leads to a mixture of products from substitution at positions 3 and 5 (XXIX, XXX) [120–122].



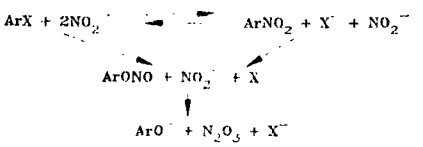
XXIX XXX

Activation of the pyridazine ring by the introduction of two N-oxide groups does not lead to an appreciable increase in the chemical activity in electrophilic substitution reactions [123, 124].

Thus, electrophilic nitration is undoubtedly useful as a method for the synthesis of nitroazines, although its possibilities have evidently already been exhausted to a significant degree. The substantial limitations due to the high π-deficiency of the azines does not make it possible to use the method for the production of polynitrogen compounds containing a nitro group.

NUCLEOPHILIC NITRATION

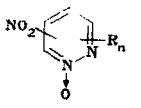
Increase in the π-deficiency of the azines, which is due to the accumulation of nitrogen atoms and complicates electrophilic substitution reactions, must assist nucleophilic nitration. In the aromatic series the synthesis of nitro compounds by the treatment of halogen derivatives by metal nitrites has hardly been used at all. The high mobility of the nitro group and the ambient character of the nitrite ion leads to the result that the nitro compound immediately undergoes attack by the NO_2^- ion, and the aromatic nitrite decomposes in reaction with NO_2^- into phenolate and N_2O_3 [125-128].

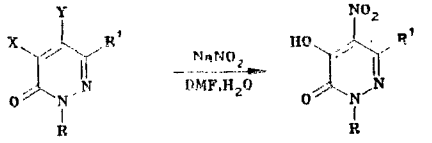


For these reasons evidently an attempt at the synthesis of nitro-1,3,5-triazine from cyanuric chloride and silver nitrite was unsuccessful [129].

At the same time, there are isolated examples of the production of nitro products by nucleophilic substitution. Thus, the 4-nitro-5-hydroxy derivatives (XXXII) are formed by the action of an excess of sodium nitrite on 4,5-dichloro(dibromo)pyridazin-6-one (XXXI) [130, 131]. In this case substitution of one of the halogen atoms by a hydroxyl in the mechanism considered above probably deactivates the molecule, and O-attack by the nitrite ion at the second nitro group does not occur.

TABLE 5. Nitropyridazine N-Oxides

	Nitration conditions	Yield, %	Reference
4-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 130°	22	111, 120
3-CH_3-4-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 100°	56	112
3-OCH_3-4-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 50°	76	118
3,6-$(CH_3)_2$-4-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 70°	83	112, 114
3-CH_3-4-NO_2-6-OCH_3	HNO_3 (*d* 1,5), H_2SO_4, 55°	81	112
3-CH_3-4-NO_2-6-Cl	HNO_3 (*d* 1,5), H_2SO_4, 90°	46	112
3-OCH_3-4-NO_2-6-Cl	HNO_3 (*d* 1,5), H_2SO_4, 55°	53	105
3-OC_2H_5-4-NO_2-6-Cl	HNO_3 (*d* 1,5), H_2SO_4, 55°	69	105
3-OCH_3-4-NO_2-5-CH_3-6-Cl	HNO_3 (*d* 1,5), H_2SO_4, 50°	88	117
3-OC_2H_5-4-NO_2-5-CH_3-6-Cl	HNO_3 (*d* 1,5), H_2SO_4, 50°	85	117
3,6-$(OCH_3)_2$-4-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 40°	59	112
3,6-$(OC_2H_5)_2$-4-NO_2	HNO_3 (*d* 1,38), H_2SO_4, 10°	40	113
3,6-$(OC_3H_7)_2$-4-NO_2	HNO_3 (*d* 1,38), H_2SO_4, 10°	30	113
3-OC_2H_5-4,6-$(NO_2)_2$	HNO_3 (*d* 1,5), H_2SO_4, 80°	25	119
3,6-$(CH_3)_2$-4-OH-5-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 20°	67	116
3-OH-4-NO_2-5-CH_3	HNO_3 (*d* 1,5), H_2SO_4, 100°	25	116
3-OH-4-CH_3-6-NO_2	HNO_3 (*d* 1,5), H_2SO_4, 50°	20	116
3-OH-4-NO_2-6-CH_3	HNO_3 (*d* 1,5), H_2SO_4, 20°	75	116
3-NO_2	C_6H_5COCl, $AgNO_3$	33	120, 121
	CH_3COCl, $AgNO_3$	17	120
3,6-$(CH_3)_2$-5-NO_2	C_6H_5COCl, $AgNO_3$	30	122

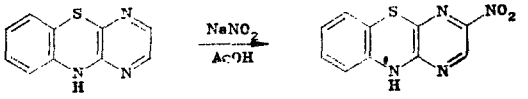


XXXI XXXII

The 2-nitro- and 5-nitropyridones were obtained during the photochemical substitution of halogen in the reaction with sodium nitrite [132].

A case is known of the substitution of a diazo group by a nitro group in guanosine with a yield of 5% by the action of nitrous acid on the latter [133].

The nucleophilic substitution of a hydrogen atom in the pyrazine fragment of the 1,4-diazaphenothiazine molecule (XXXIII) was described in [134].



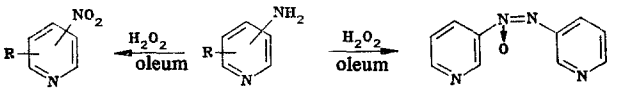
XXXIII

The reaction includes the stage of oxidation of XXXIII by nitrous acid to the cation and attack by the nitrite ion.

OXIDATION OF AMINO AND NITROSO GROUPS

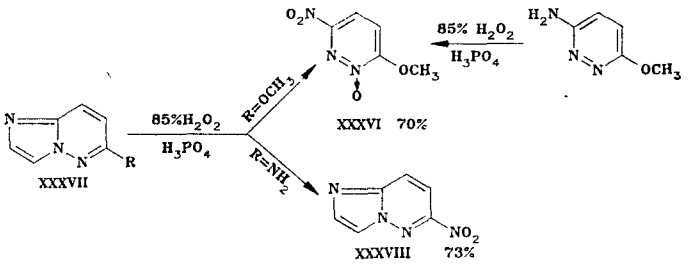
The production of nitro compounds by the oxidation of amino and nitroso derivatives is mainly employed in the aromatic series [135]. Such a method has been used little for the synthesis of heterocyclic nitro compounds, although it is fairly useful and in some cases more effective than other methods.

Good results have been obtained for pyridine derivatives, but the reaction does not take place in a well-defined manner; the corresponding nitro products XXXIV have been obtained from 2- and 4-aminopyridines [136-139], and the azoxy compounds (XXXV) was obtained during the oxidation of 3-aminopyridine [139].

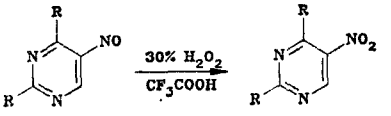


XXXIV XXXV

In the series of aminodiazines only nitropyridazines have been obtained by the oxidation of amino groups. 3-Nitro-6-methoxypyridazine N-oxide (XXXVI) is formed during the action of a mixture of 85% hydrogen peroxide in phosphoric acid on the corresponding amino derivatives [140]. During treatment of 6-methoxyimidazo[1,2-b]pyridazine (XXXVII, R=OCH_3) with this mixture the imidazole ring is destroyed, and compound (XXXVI) is formed. In this reaction 6-aminoimidazo[1,2-b]pyridazine (XXXVII, R=NH_2) gives the 6-nitro product (XXXVIII).



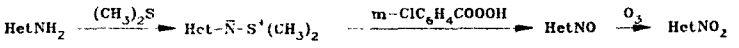
The production of 5-nitropyrimidines (XXXIX) by the oxidation of the nitroso derivatives with 30% hydrogen peroxide in trifluoroacetic acid is also known [141].



XXXIX

R=Alk, Ar, OH, NH_2

It should be noted that these methods have not become widely used on account of the need to use concentrated solutions of hydrogen peroxide, the possibility of side processes, and the limited availability of the nitrosoazines. It is true, the recently described original method [142] for the transformation of amines into nitroazines, including the oxidation of the nitroso group, makes it possible to approach this problem more optimistically:



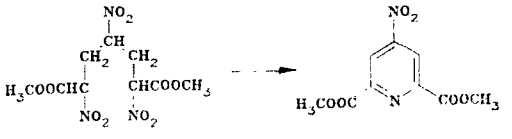
Het = 2-pyridyl, 1-isoquinolyl, 2-pyrimidinyl, 2-pyrazinyl

CYCLIZATION OF ALIPHATIC NITRO SYNTHONS

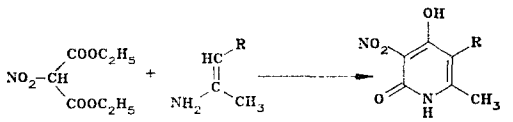
The formation of heterocyclic compounds from nitro precursors with an open chain has a series of advantages over other methods. In this case it is possible to produce compounds which are inaccessible by direct nitration and contain one, two, or three nitrogen atoms in the ring with the substituents in a known arrangement and to preserve groups which could be destroyed under the conditions of nitration or oxidation. Various types of aliphatic nitro compounds containing two reaction centers have been used in such syntheses, but nitrocarbonyl derivatives occupy a special position.

Nitropyridines. Several methods involving the formation of both C—N and C—C bonds have been developed for the synthesis of nitropyridines and their condensed analogs from aliphatic nitro compounds, introducing five, three, or two carbon atoms into ring formation (C_5, C_3, and C_2 nitro synthons).

The transformation of 1,5-dimethoxycarbonyl-1,3,5-trinitropentane into dimethyl 4-nitropyridine-2,6-dicarboxylate can be regarded as an example of the use of the C_5 nitro synthons [143].



The derivatives of nitromalonic acid are included among the C_3 nitro synthons. The diethyl ester of this acid, nitromalonic ester (NME), makes it possible to obtain substituted 3-nitropyridines (XL) in one stage [144]:



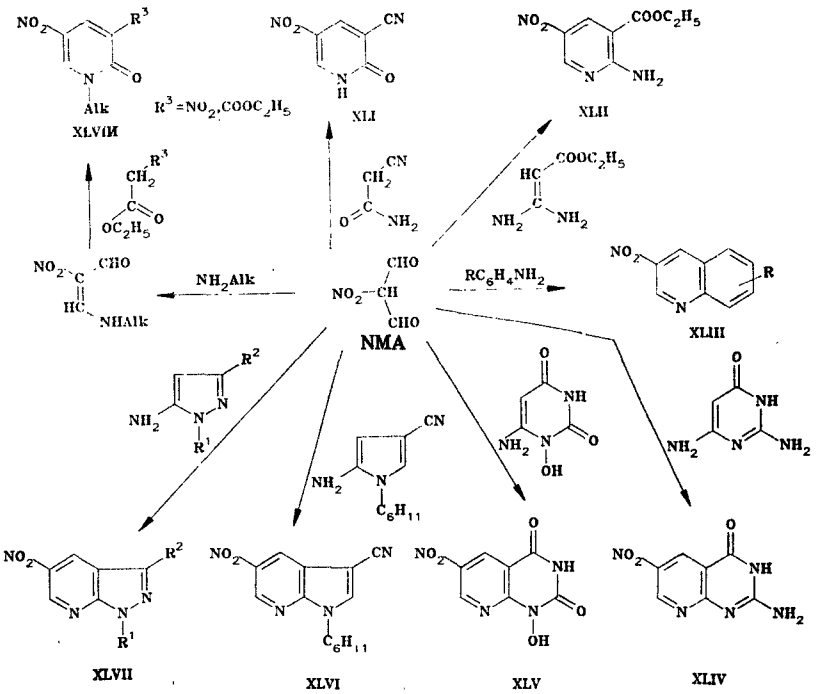
NME XL

Nitromalonaldehyde (NMA) gives wider possibilities. The 3-nitropyridines, also obtained from this nitro synthon in a single stage, are given in Scheme 1. The condensation of NMA with cyanoacetamide or aminoacrylic esters leads to the formation of 3-cyano- or 3-ethoxy carbonyl-5-nitropyridine (XLI) or (XLII) [145-148].

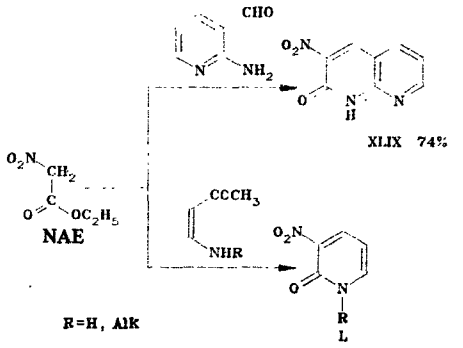
Derivatives of 3-nitroquinoline (XLIII) unobtainable by direct nitration were obtained with good yields from NMA and substituted anilines [149]. 6-Nitropyrimido[4,5-b]pyridines (XLIV, XLV) were obtained from aminopyrimidines by a similar method [150, 151]. Aminoazoles also enter into reaction with NMA. Pyrrolo[2,3-b]pyridine (XLVI) [152] and 5-nitropyrazolo [3,4-b]pyridines (XLVII) [153] were obtained in this way.

In reaction with malonic or nitroacetic esters the products from the condensation of NMA with amines (α-nitro-o-alkylaminoacroleins) give 3-ethoxycarbonyl-5-nitro- and 3,5-dinitro-2-pyridones (XLVIII) [154, 155].

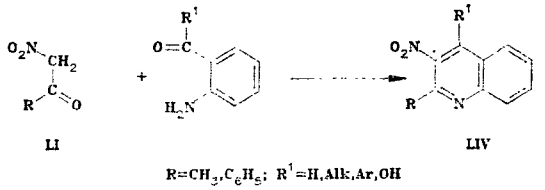
Scheme 1



Another direction in the synthesis of nitropyridines is the construction of the pyridine ring from nitrocarbonyl compounds supplying two carbon atoms, e.g., nitroacetic ester (NAE), α-nitro ketones, derivatives of nitroethylene, and others. 3-Nitro-1,8-naphthirid-2-one (XLIX) [156], and 3-nitropyridones (L) were obtained by the reaction with aminoethylene derivatives [156, 157].



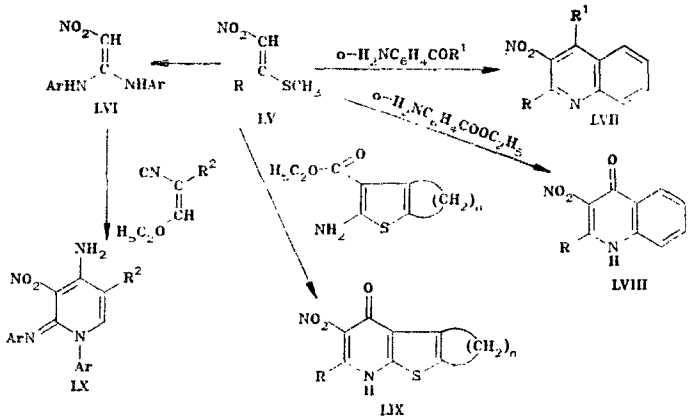
Reacting in a similar scheme, nitroacetone and nitroacetophenone (LI) give nitroquinolines (LIV) with o-aminobenzaldehyde (LII) and o-aminoacetophenone (LIII) [158, 159].



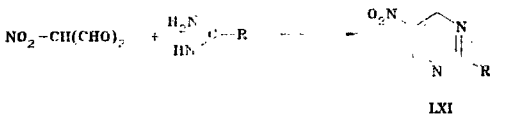
Nitroquinolines (LIV) (R = H) are also formed in the reaction of (LII) and (LIII) with the readily obtainable nitroacetaldehyde oxime (metazonic acid) [159-162].

Alkylthio and amino derivatives of nitroethylene (LV, LVI) have recently found wide use as C_2-nitro synthons, from which annellated (LVII—LIX) and monocyclic (LX) nitropyridines were obtained with good yields [163-166] (Scheme 2).

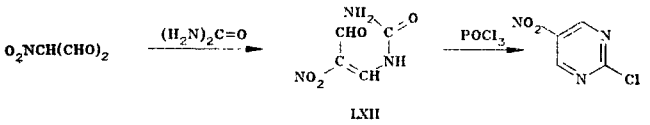
Scheme 2



Nitropyrimidines. The previously examined methods have found much greater significance in the construction of nitrodiazine and nitrotriazine systems. The condensation of β-dicarbonyl nitro compounds (C_3-nitro synthons) with amidines has found wide use in the synthesis of nitropyrimidines. Thus, 2-substituted 5-nitropyrimidines (LXI) are formed smoothly in their reaction with NMA [167-174].

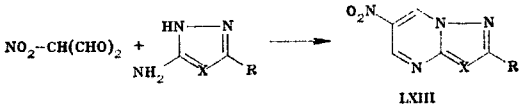


The yields vary between 30 and 90%, and the 2-alkyl-substituted compounds are obtained with small yields. Arylamidines react better [172], while the condensation of guanidine with NMA goes quantitatively [168, 169, 173]. The reaction with urea leads to the open-chain product (LXII) and, then, after treatment with phosphorus oxychloride to 2-chloro-5-nitropyrimidine [175].



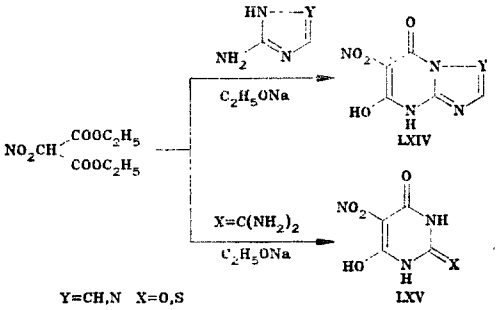
LXII

Condensation with thiourea or isothiouronium salts in the presence of piperidine gives 2-piperidino-5-nitropyrimidine, and with diethylamine or sodium hydroxide as catalyst it gives the 2-thio derivatives [172, 176–178].



LXIII

The characteristic analogs of the amidines (aminoazoles) react with NMA to form 6-nitroazolo[1,5-a]pyrimidines (LXIII) [179].



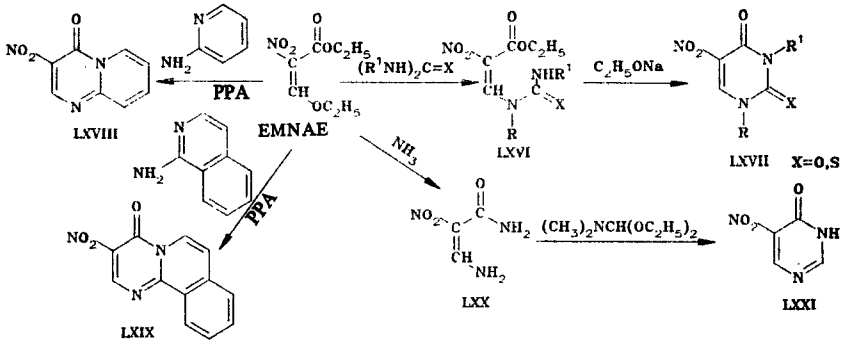
LXIV

LXV

Y=CH,N X=O,S

A convenient method for the production of azolopyrimidines (LXIV) is the reaction of 2-aminoimidazole [180] and 3-aminotriazole [181] with NME. The use of urea and thiourea instead of the azoles gave 5-nitrobarbituric and 2-thio-5-nitrobarbituric acids (LXV) [75, 182, 183].

Scheme 3



LXVIII

LXIX

LXVI

LXVII X=O,S

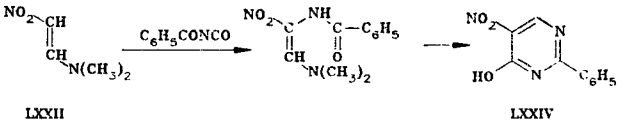
LXX

LXXI

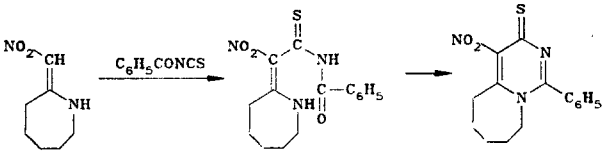
A C_3-nitro synthon such as ethoxymethylenenitroacetic ester (EMNAE, Scheme 3) has found use in the synthesis of nitropyrimidines. When treated with sodium ethoxide, the ureidomethylenenitroacetic esters (LXVI) formed in the condensation of EMNAE with urea or thiourea give the corresponding 5-nitrouracils (LXVII) [184, 185]. The synthesis of 3-nitro-4-oxo-4H-pyrido[1,2-a]pyrimidine (LXVIII) and 3-nitro-1-oxo-4H-pyrimido[2,1-a]isoquinoline (LXIX)

by a similar scheme has been described [18]. The treatment of EMNAE with ammonia gives α-nitro-β-aminoacrylamide (LXX), the reaction of which with dimethylformamide diethyl acetal gives 4-hydroxy-5-nitropyrimidine (LXXI) [186].

In addition to the above-mentioned methods in which β-dicarbonylnitro compounds are employed there are examples of the synthesis of nitropyrimidines involving the use of C_2-nitro synthons. Thus, 2-phenyl-4-hydroxy-5-nitropyrimidine (LXXIV) [187] and 2-phenyl-4-thio-5-nitrohexahydroazepino[1,2-c]pyrimidine (LXXV) [188] were obtained from α-amino-β-nitroethylenes (LXXII, LXXIII).

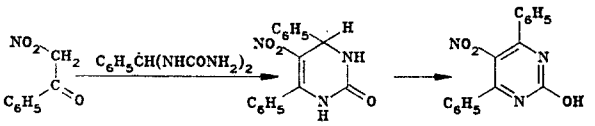


LXXII LXXIV



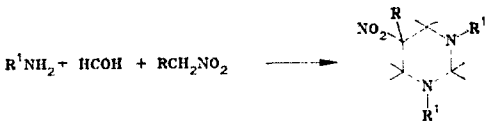
LXXIII LXXV

Nitroacetophenone has been used [189] for the construction of the dihydropyrimidine ring containing a nitro group (LXXVI). Compound (LXXVI) is readily dehydrogenated by bromination–debromination to 2-hydroxy-4,6-diphenyl-5-nitropyrimidine (LXXVII).



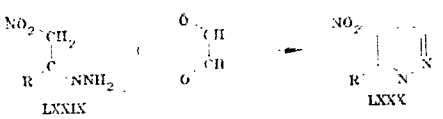
LXXVI LXXVII

Hydrogenated 5-nitropyrimidines (LXXVIII) can be easily obtained in the Mannich reaction [190–192].



R,R¹=H, Alk LXXVIII

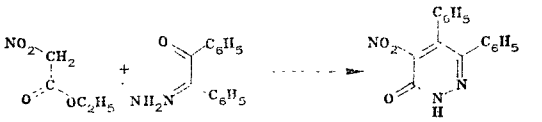
Nitropyridazines. The main method for the synthesis of nitropyridazines involves the condensation of C_2-nitrocarbonyl compounds with derivatives of glyoxal, where the nitrogen atoms used for the construction of the ring are introduced both as one and as the other components. Thus, 4-nitropyridazines (LXXX) are formed with yields of 40-50% in the reaction of the hydrazones (LXXIX), which are in turn obtained from 1-nitro-2,2-dimethylthio- or 1-nitro-2-amino-2-methylthioethylene, with glyoxal [193].



LXXIX LXXX

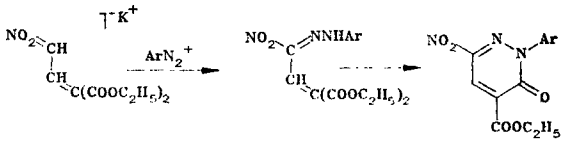
R=SCH_3, NHC_6H_5, $NHCH_2C_6H_5$, 2-adamantylamino

A unique version of this synthesis is the condensation of NAE with diphenylglyoxal monohydrazone [194, 195]:



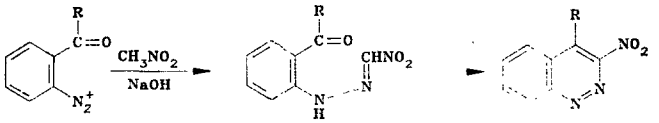
39%

An accessible synthesis of 1-aryl-3-nitropyridazines (LXXXI) was proposed in [196]; the coupling of diazonium salts with the products from the condensation of 1-dimethylamino-2-nitroethylene and malonic ester (LXXXII) leads to the arylhydrazones (LXXXIII) and then to the nitropyridazines (LXXXI).



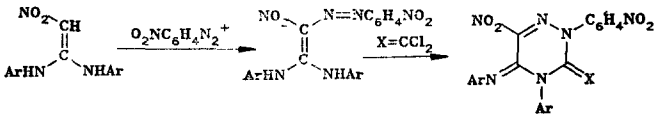
LXXXII LXXXIII LXXXI

The production of 3-nitrocinnolines (LXXXIV) can be regarded as the only case of the use of a C_1-nitro synthon [197, 198]:



R=H,CH_3 LXXXIV

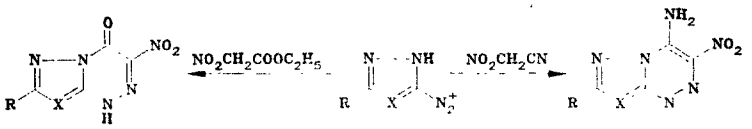
Nitrotriazines. The high π-deficiency of the triazine system fully excludes electrophilic nitration [199], and the cyclization of aliphatic nitro compounds becomes the only suitable but still undeveloped method for the synthesis of 1,2,4-triazines. The production of triazines (LXXXV) with yields of 65–95% by the action of phosgene, thiophosgene, or dichloromethylenesulfonamide on 1-nitro-1-arylazo-2,2-diarylaminoethylene (LXXXVI) was described in [200].



LXXXVI LXXXV

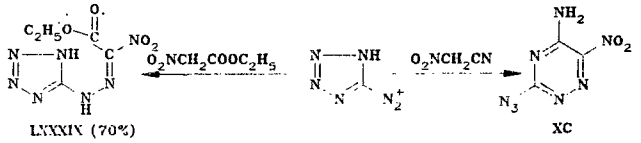
X=O, S, $NSO_2C_6H_5$

The construction of condensed nitro-1,2,4-triazine rings from β-nitrocarbonyl compounds and diazoazoles was proposed in [201, 202].



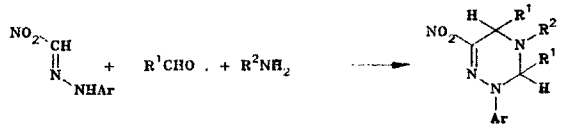
LXXXVII R=H,Alk,Ar; X=N,CR LXXXVIII

A series of 6-nitro-7-oxo-4,7-dihydroazolo[5,1-c][1,2,4]triazines (LXXXVII) were obtained by coupling diazopyrazoles and diazotriazoles with NAE in an alkaline medium. In the reaction of NAE with diazotetrazole under these conditions the reaction stops at the stage of the hydrazone (LXXXIX). The condensation of diazoazoles with nitroacetonitrile leads to the formation of nitroaminotriazines (LXXXVIII) and (XC).



LXXXIX (70%) XC

Substituted 6-nitro-2,3,4,5-tetrahydro-1,2,4-triazines (XCI) can be easily obtained under the conditions of the Mannich reaction from nitroformaldehyde arylhydrazones [203–205].



XCI

Syntheses of 1,3,5-triazines containing a nitro group are unknown.

Thus, analysis of the literature has shown that the appearance of new accessible starting materials, new methods of synthesis, and new experimental methods has stimulated the chemistry of heterocyclic nitro compounds, including nitroazines.

LITERATURE CITED

1. Zh. I. Aksel'rod and V. M. Berezovskii, Usp. Khim., 39, 1337 (1970).
2. J. H. Ridd, Z. Chem., 8, 201 (1968).
3. K. Schofield, Quart. Rev., 4, 382 (1950).
4. S. Rajappa and M. D. Nair, Adv. Heterocycl. Chem., 25, 113 (1979).
5. D. J. Brown, in: The Pyrimidines, Wiley, New York–London–Sydney (1962).
6. M. Tišler and B. Stanovnik, Adv. Heterocycl. Chem., 9, 211 (1968).
7. M. Tišler and B. Stanovnik, Adv. Heterocycl. Chem., 24, 363 (1978).
8. L. Novacek, K. Palat, and M. Celadnik, Chem. Listy, 57, 299 (1963).
9. H. J. Den Hertog and J. Overhoff, Rec. Trav. Chim., 49, 552 (1930).
10. C. D. Johnson, A. R. Katritzky, and M. Viney, J. Chem. Soc., B, No. 11, 1211 (1967).
11. M. M. Boudakian, U.S. Patent No. 4310671; Ref. Zh. Khim., 21N128 (1982).
12. A. R. Katritzky, H. O. Tarhan, and S. Tarhan, J. Chem. Soc., B, No. 1, 114 (1970).
13. A. G. Burton, P. J. Halls, and A. R. Katritzky, J. Chem. Soc., Perkin Trans. II, No. 13, (1972).
14. A. G. Burton, R. D. Frampton, C. D. Johnson, and A. R. Katritzky, J. Chem. Soc., Perkins Trans. II, No. 13, 1940 (1972).
15. G. Bianchi, A. G. Burton, C. D. Johnson, and A. R. Katritzky, J. Chem. Soc., Perkin Trans. II, No. 13, 1950 (1972).
16. A. R. Katritzky and B. J. Ridgewell, J. Chem. Soc., No. 7, 3753 (1963).
17. Y. Morisava, M. Kataoka, N. Kitano, and T. Matsuzawa, Patent No. 2536202 (BRD); Chem. Abs., 85, 5507 (1976).
18. E. Plazek, Berichte, 72, 577 (1939).
19. E. V. Brown and R. H. Neil, J. Org. Chem., 26, 3546 (1961).
20. L. Achremowicz, T. Batkowski, and Z. Skrowaczewska, Roczn. Chem., 38, 1317 (1964).
21. L. N. Pino and W. S. Zehrung, J. Am. Chem. Soc., 77, 3154 (1955).
22. A. Thomas, P. Tomasnik, and G. Herman-Matusiak, Bull. Acad. Pol. Sci., Ser. Sci. Chim., 23, 311 (1975).
23. H. Kokosinska, A. Thomas, P. Tomasik, and R. Zalewski, Bull. Acad. Pol. Sci., Ser. Sci. Chim., 24, 535 (1976).
24. L. W. Deady, M. R. Grimmot, and C. H. Potts, Tetrahedron, 35, 2895 (1979).
25. E. Plazek, A. Marcinikow, and Ch. Stammer, Roczn. Chem., 15, 365 (1935); Chem. Abs., 30, 1377 (1936).
26. G. P. Sharnin, I. F. Falyakhov, and F. G. Khairutdinov, Khim. Geterotsikl. Soedin., No. 3, 363 (1980).
27. G. P. Sharnin, I. F. Falyakhov, and F. G. Khairutdinov, Khim. Geterotsikl. Soedin., No. 12, 1632 (1980).

28. A. G. Burton, R. D. Frampton, C. D. Johnson, and A. R. Katritzky, J. Chem. Soc., Perkin Trans. II, No. 13, 1943 (1972).
29. E. Haack, German Patent No. 568549; Chem. Abs., 27, 2697 (1933).
30. C. Räth, Annalen, 484, 52 (1930).
31. A. H. Berrie, G. T. Newbold, and F. S. Spring, J. Chem. Soc., No. 10, 2590 (1951).
32. J. Kozlowska and E. Plazek, Roczn. Chem., 33, 831 (1959).
33. C. A. Salemink and G. M. can der Want, Rec. Trav. Chim., 68, 1013 (1949).
34. M. D. Coburn, J. Heterocycl. Chem., 11, 1099 (1974).
35. R. C. De Selms, J. Org. Chem., 33, 478 (1968).
36. L. D. Smirnov, R. E. Lokhov, V. P. Lezina, B. E. Zaitsev, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1567 (1969).
37. K. M. Dyumaev and L. D. Smirnov, Usp. Khim., 44, 1788 (1975).
38. J. Bernstein, B. Stearns, E. Shaw, and W. A. Lott, J. Am. Chem. Soc., 69, 1151 (1947).
39. H. J. Den Hertog, C. Jouwersma, A. A. van der Wal, and E. C. C. Willebrands-Schogt, Rec. Trav. Chim., 68, 275 (1949).
40. E. Koenigs, H. C. Gerdes, and A. Sirot, Berichte, 61, 1022 (1928).
41. E. Koenigs and A. Fulde, Berichte, 60, 2106 (1927).
42. W. Gzuba and E. Plazek, Rec. Trav. Chim., 77, 92 (1958).
43. K. V. Rao and P. Venkateswarlu, J. Heterocycl. Chem., 12, 731 (1975).
44. F. Kögl, G. M. van der Want, and C. A. Salemink, Rec. Trav. Chim., 67, 29 (1948).
45. L. N. Yakhontov, M. Ya. Uritskaya, V. A. Loginova, and M. V. Rubtsov, Khim. Geterotsikl. Soedin., No. 3, 456 (1969).
46. L. D. Smirnov and K. M. Dyumaev, Khim. Geterotsikl. Soedin., No. 9, 1155 (1976).
47. W. H. Crowe, J. Chem. Soc., No. 9, 2028 (1925).
48. S. Kruger and F. G. Maun, J. Chem. Soc., No. 8, 2755 (1955).
49. S. Caldwell and C. E. Martin, J. Heterocycl. Chem., 17, 989 (1980).
50. R. F. Evans and W. Kynaston, J. Chem. Soc., No. 12, 5556 (1961).
51. R. B. Brown, J. Am. Chem. Soc., 79, 3565 (1957).
52. G. C. Wright, U.S. Patent No. 4216327; Ref. Zh. Khim., 50107 (1981).
53. H. J. den Hertog, M. van Ammers, and S. Schukking, Rec. Trav. Chim., 74, 1171 (1955).
54. H. J. Den Hertog, C. H. Henkens, and K. Dilz, Rec. Trav. Chim., 72, 296 (1953).
55. C. D. Johnson, A. R. Katritzky, N. Shakir, and M. J. Viney, J. Chem. Soc., B, No. 11, 1213 (1967).
56. G. P. Bean, P. J. Brignell, C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, H. O. Tarhan, and A. M. White, J. Chem. Soc., B, No. 11, 1222 (1967).
57. W. A. Lott and E. Shaw, J. Am. Chem. Soc., 71, 70 (1949).
58. H. J. Den Hertog and M. van Ammers, Rec. Trav. Chim., 74, 1160 (1955).
59. M. Van Ammers and H. J. Den Hertog, Rec. Trav. Chim., 75, 1259 (1956).
60. R. Lewicka and E. Plazek, Rec. Trav. Chim., 78, 644 (1959).
61. M. J. S. Dewar and P. M. Maitlis, J. Chem. Soc., No. 6, 2521 (1957).
62. D. H. G. Grant, J. R. Penton, and K. Schofield, J. Chem. Soc., B, No. 6 1254 (1971).
63. K. M. Dyumaev, E. P. Popova, I. F. Mikhailov, A. I. Shibaeva, and L. D. Smirnov, Khim. Geterotsikl. Soedin., No. 6, 805 (1974).
64. K. Schofield and T. Swuin, J. Chem. Soc., No. 5, 1367 (1949).
65. B. B. Moodie, J. R. Penton, and K. Schofield, J. Chem. Soc., B, No. 7, 1493 (1971).
66. M. J. S. Dewar and P. M. Maitlis, J. Chem. Soc., No. 3, 944 (1957).
67. M. Ikehara and G. Shimizu, Chem. Pharm. Bull., 7, 501 (1959).
68. H. E. Foster and J. Hurst, J. Chem. Soc., Perkin Trans I, No. 23, 2901 (1973).
69. Yu. M. Yutilov and I. A. Svertilova, Khim. Geterotsikl. Soedin., No. 5, 705 (1982).
70. R. M. Bystrova and Yu. M. Yutilov, Khim. Geterotsikl. Soedin., No. 6, 953 (1968).
71. B. M. Lynch and B. P. L. Lom, J. Heterocycl. Chem., 11, 223 (1974).
72. W. W. Paudler and J. N. Chasman, J. Heterocycl. Chem., 10, 499 (1973).
73. J. D. Tedlade, R. Escale, G. Grassy, J. P. Girard, and J. P. Chapat, Bull. Soc. Chim. France, Part 2, No. 9-10, 529 (1979).
74. G. Saint-Ruf, B. Loukakou, and C. N'Zouzi, J. Heterocycl. Chem., 18, 1565 (1981).
75. R. Nutiu and I. Sebe, Rev. Roum. Chim., 16, 919 (1971).
76. D. J. Brown, J. Appl. Chem., 2, 239 (1952).
77. R. A. Ling, T. R. Matthews, and R. K. Robins, J. Med. Chem., 19, 1072 (1976).
78. C. D. Johnson and A. R. Katritzky, J. Chem. Soc., No. 1, (1971).
79. D. E. O'Brien, C. C. Cheng, and S. Pfleiderer, J. Med. Chem., 9, 573 (1966).
80. D. J. Brown, J. Soc. Chem. Ind., 69, 353 (1950).
81. D. J. Brown, Proc. Royal. Aust. Chem. Inst., 33, 57 (1966).

82. I. Wempen, H. U. Blank, and J. J. Fox, J. Heterocycl. Chem., 6, No. 4, 593 (1969).
83. K. Baeyer, Annalen, 127, 199 (1863).
84. W. Trcinski, Berichte, 16, 1057 (1883).
85. H. Blitz and K. Sédlatscheck, Berichte, 57, 339 (1924).
86. R. Bartling, Annalen, 339, 37 (1905).
87. K. Baeyer, Annalen, 135, 312 (1865).
88. D. J. Brown, J. Appl. Chem., 9, 203 (1959).
89. D. J. Brown, J. Appl. Chem., 7, 109 (1957).
90. D. J. Brown, E. Hoeger, and S. F. Mason, J. Chem. Soc., No. 1, 211 (1955).
91. J. L. Rabinowitz and S. Gurin, J. Am. Chem. Soc., 75, 5758 (1953).
92. C. Cenda, H. Idzumi, and M. Kano, Annu. Proc. Coll. Pharmacy, No. 11, 62 (1961). Ref. Zh. Zhim., 24Zh362 (1962).
93. R. K. Robins, F. W. Furcht, A. D. Grauer, and J. W. Jonnes, J. Am. Chem. Soc., 78, 2418 (1956).
94. H. Kano and T. Makimsumi, Japanese Patent No. 5946; Ref. Zh. Khim., 14N281 (1964).
95. Y. Makisumi, Chem. Pharm. Bull., 9, 873 (1961).
96. B. M. Lynch, M. A. Khan, S. C. Sharma, and H. C. Teo, Can. J. Chem., 53, 119 (1975).
97. A. Ohta, T. Watanabe, Y. Akita, and T. Kurihara, Hukusokau Kagaku Toronkai Koen Yoshishu, 84 (1975); Chem. Abs., 84, 164723 (1976).
98. G. Karmas and P. E. Spoerri, J. Am. Chem. Soc., 75, 5517 (1953).
99. G. Karmas and P. E. Spoerri, J. Am. Chem. Soc., 78, 4071 (1956).
100. D. S. Donald, U.S. Patent No. 3808209; Ref. Zh. Khim., 7N246 (1975).
101. S. Dikson and L. F. Wiggins, J. Chem. Soc., No. 10, 3235 (1950).
102. T. Itai and S. Suzuki, Chem. Pharm. Bull., 8, 999 (1960).
103. D. L. Aldous and R. N. Castle, Arzneimittel Forsch., 13, 878 (1963).
104. W. D. Guinther, D. G. Clark, and R. N. Castle, J. Heterocycl. Chem., 2, 67 (1965).
105. M. Yanai, T. Kinoshita, S. Takeda, H. Sadaki, and H. Watanabe, Chem. Pharm. Bull., 18, 1680 (1970).
106. R. D. Thompson and R. N. Castle, J. Heterocycl. Chem., 18, 1523 (1981).
107. H. E. Baumgarten, J. Am. Chem. Soc., 77, 5109 (1955).
108. T. Terai, H. Azuma, and R. Hattori, Japanese Patent No. 1299; Chem. Abs., 66, 65499 (1967).
109. T. Terai, H. Azuma, and R. Hattori, Japanese Patent No. 1300; Chem. Abs., 66, 65497 (1967).
110. M. Takay, K. Terashima, and K. Ozeki, Takugaku Zasshi, 98, 1472 (1978); Chem. Abs., 90, 152105 (1979).
111. T. Itai and S. Natsume, Chem. Pharm. Bull., 11, 83 (1963).
112. T. Nakagome, Yakugaku Dzassi, 82, 253 (1962); Ref. Zh. Khim., 1963, 8Zh281.
113. T. Itai and S. Sako, Chem. Pharm. Bull., 9, 149 (1961).
114. S. Sako, Chem. Pharm. Bull., 11, 337 (1963).
115. T. Itai and S. Sako, Chem. Pharm. Bull., 14, 269 (1966).
116. H. Igeta, T. Tsuciya, M. Nakajima, T. Seikya, Y. Kumaki, T. Nakai, and T. Nojima, Chem. Pharm. Bull., 17, 756 (1969).
117. P. D. Cook and R. N. Castle, J. Heterocycl. Chem., 10, 551 (1973).
118. H. Igeta, Chem. Pharm. Bull., 8, 550 (1960).
119. M. Yanai, T. Kinoshita, and S. Takeda, Chem. Pharm. Bull., 19, 2181 (1971).
120. T. Itai and S. Natsume, Chem. Pharm. Bull., 11, 342 (1963).
121. T. Itai and S. Natsume, Chem. Pharm. Bull., 12, 223 (1964).
122. S. Kamjya and M. Tanno, Chem. Pharm. Bull., 23, 923 (1975).
123. M. Nakadate, S. Sueyoshi, and S. Suzuki, Chem. Pharm. Bull., 18, 1211 (1970).
124. S. Sueyoshi and I. Susuki, Chem. Pharm. Bull., 23, 2772 (1975).
125. D. H. Rosenblat, W. H. Dennis, and R. D. Goodin, J. Am. Chem. Soc., 95, 2133 (1973).
126. T. J. Broxton, D. M. Muir, and A. J. Parker, J. Org. Chem., 40, 2037 (1975).
127. T. J. Broxton, D. M. Muir, and A. J. Parker, J. Org. Chem., 40, 3230 (1975).
128. V. A. Ustinov, V. V. Plakhtinskii, G. S. Mironov, and N. S. Ryabukhina, Zh. Org. Khim., 25, 1775 (1979).
129. H. Finger, J. Prakt. Chem., 75, 103 (1907).
130. N. B. Galstukhova, G. S. Predvoditeleva, I. M. Berzina, T. Yu. Kartseva, M. N. Shchukina, and G. N. Pershin, Khim.-Farm. Zh., No. 4, 7 (1969).
131. F. Reicheneder and K. Dury, French Patent No. 1384304; Chem. Abs., 62, 16265 (1965).
132. A. N. Frolov, A. V. El'tsov, and O. V. Kul'bitskaya, Khim. Geterotsikl. Soedin., No. 12, 1645 (1974).
133. R. Shaipro, J. Am. Chem. Soc., 84, 2948 (1964).
134. S. D. Carter and G. W. H. Cheesman, Tetrahedron, 33, 827 (1977).
135. H. M. Feuer (editor), Chemistry of the Nitro and Nitrose Groups, Wiley (1970).

136. W. D. Emmons, J. Am. Chem. Soc., 79, 5528 (1957).
137. E. Brown, J. Am. Chem. Soc., 76, 3167 (1954).
138. A. Kirpal and W. Böhm, Berichte, 65, 680 (1932).
139. R. H. Wiley and I. L. Hertman, J. Am. Chem. Soc., 73, 494 (1951).
140. B. Stanovnik, M. Tisler, and A. Pollak, J. Org. Chem., 35, 2478 (1970).
141. E. C. Taylor and A. McKillop, J. Org. Chem., 30, 3153 (1965).
142. E. C. Taylor, Tseng Chi-Ping, and J. B. Rampal, J. Org. Chem., 47, 552 (1982).
143. A. Garming, D. Redwan, P. Gelbke, D. Kern, and U. Direks, Annalen, No. 7, 1744 (1975).
144. A. Dornow and H. von Plesen, Chem. Ber., 99, 244 (1966).
145. P. E. Fanta and R. A. Stein, J. Am. Chem. Soc., 77, 1045 (1955).
146. P. F. H. Freeman, U. S. Patent No. 3674877; Chem. Abs., 77, 88314 (1972).
147. P. E. Fanta, J. Am. Chem. Soc., 75, 737 (1953).
148. D. J. Collins, J. Chem. Soc., No. 2, 1337 (1963).
149. P. E. Fanta and R. A. Stein, Chem. Rev., 60, 261 (1960).
150. T. C. Lee and G. Salemnik, J. Org. Chem., 40, 3608 (1975).
151. R. Bernetti, F. Mansini, and C. C. Price, J. Org. Chem., 27, 2863 (1962).
152. A. Broderick and D. G. Wibberley, J. Chem. Soc., Perkin Trans I, No. 10, 1910 (1975).
153. V. L. Rusinov, A. Yu. Petrov, and I. Ya. Postovskii, in: Chemistry of Dicarbonyl Compounds [in Russian], Riga (1981), p. 195.
154. S. M. Kvitko, V. V. Perekalin, and N. V. Buival, Zh. Org. Khim., 2, 2253 (1966).
155. Yu. V. Maksimov and S. M. Kvitko, in: Some Aspects of the Chemistry of Rare-Earth Elements [in Russian], Barnaul'skii Pedinstitut, Barnaul (1975), p. 58.
156. E. M. Hawes and D. G. Wibberley, J. Chem. Soc. C, No. 3, 315 (1966).
157. Zh. A. Krasnaya, T. S. Statsenko, E. P. Prokof'ev, I. P. Yakovlev, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 4, 845 (1974).
158. A. Dornow and W. Sassenberg, Annalen, 602, 14 (1957).
159. H. E. Baumgarten and J. L. Saylor, J. Am. Chem. Soc., 79, 1502 (1957).
160. D. W. Ockenden and K. Schofield, J. Chem. Soc., No. 12, 3914 (1953).
161. K. Schofield and R. S. Theobald, J. Chem. Soc., No. 1, 395 (1950).
162. G. B. Bryant, D. E. Wolton, G. L. Jenkins, and J. E. Christian, J. Am. Chem. Soc., 69, 365 (1947).
163. H. Schäfer, K. Gewald, and M. Seifert, J. Prakt. Chem., 318, 39 (1976).
164. H. Schäfer, B. Bartho, and K. Gewald, Z. Chem., 13, 294 (1973).
165. H. Schäfer and K. Gewald, Z. Chem., 18, 335 (1978).
166. H. Schäfer and K. Gewald, Z. Chem., 16, 272 (1976).
167. W. J. Hale and H. C. Brill, J. Am. Chem. Soc., 34, 82 (1912).
168. R. O. Robin, R. S. Winnek, and J. P. Englisch, J. Am. Chem. Soc., 64, 567 (1942).
169. P. E. Fanda and E. A. Hedman, J. Am. Chem. Soc., 78, 1434 (1956).
170. M. P. L. Caton, D. T. Hurst, J. F. W. McOmie, and R. R. Hunt, J. Chem. Soc. C, No. 13, 1204 (1967).
171. D. T. Hurst and J. Christophides, Heterocycles, 6, 1999 (1977).
172. R. Andrisano and G. Modena, Bull. Sci. Fac. Chim. Int. Bologna, 10, 156 (1952); Chem. Abs., 47, 4737 (1953).
173. Y. Rahamin, J. Sharvit, A. Mandelbaum, and M. Sprecher, J. Org. Chem., 32, 3856 (1967).
174. A. Guiliana, L. Bernardi, M. Foglio, A. Glaesser, and H. Temperilli, Pat. 2259012 (BRD); Chem. Abs., 79, 53660 (1973).
175. M. P. V. Boarland and J. F. W. McOmie, J. Chem. Soc., No. 3, 1218 (1951).
176. M. P. L. Caton and J. F. W. McOmie, J. Chem. Soc., C, No. 7, 836 (1968).
177. Yu. V. Maksimov, in: Some Aspects of the Chemistry of Rare-Earth Elements [in Russian], Barnaul'skii Pedinstitut, Barnaul (1975), p. 86.
178. Yu. V. Maksimov and V. N. Aleinikov, in: Some Aspects of the Chemistry of Rare-Earth Elements [in Russian], Barnaul'skii Pedinstitut, Barnaul (1975), p. 75.
179. V. L. Rusinov, I. Ya. Postovskii, A. Yu. Petrov, E. O. Sidorov, and Yu. A. Azev, Khim. Geterotsikl. Soedin., No. 11, 1554 (1981).
180. D. E. O'Breien, R. K. Robins, and L. N. Simon, U. S. Patent No. 3907799; Chem. Abs., 84, 4998 (1976).
181. Y. Makisumi, Chem. Pharm. Bull., 9, 801 (1961).
182. R. Nutiu and I. Sebe, Rev. Roum. Chim., 16, 919 (1971).
183. R. Nutiu, I. Sebe, and M. Nutiu, Rev. Roum. Chim., 19, 860 (1974).
184. O. S. Wolfbeis, Chem. Ber., 100, 2480 (1977).
185. M. Prystas and J. Gut, 28, 2501 (1963).
186. H. Vorbrüggen and P. Strehlke, Chem. Ber., 106, 3030 (1973).

187. G. Simchen, Angew Chem., 19, 860 (1964).
188. S. Rajappa, R. Sreenivasan, B. G. Advani, R. H. Summerville, and R. Hoffmann, Indian J. Chem., 15B, 297 (1977).
189. Z. D. Dubovenko and V. P. Mamaev, Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk, No. 3, 101 (1972).
190. T. Urbanski, Z. Bierncki, and E. Lipska, Roczn. Chem., 28, 169 (1954).
191. T. Urbanski and E. Lipska, Roczn. Chem., 26, 182 (1952).
192. H. Artus, "Über acyklische und heterocyclische Alkylation und Amino-alkylation," Dissertation, Hamburg (1977).
193. T. Severin, B. Brück, and P. Adhikary, Chem. Ber., 99, 3097 (1966).
194. A. Aydin and H. Feuer, Chim. Acta Turcica, 7, 121 (1979).
195. A. Aydin and H. Feuer, Chim. Acta Turcica, 9, 199 (1981).
196. H. Hamberger, H. Reinshagen, G. Schulz, and G. Sigmund, Tetrahedron Lett., No. 41, 3619 (1977).
197. H. E. Baumgarten and M. R. DeBruner, J. Am. Chem. Soc., 76, 3489 (1954).
198. H. E. Baumgarten and D. L. Pederson, J. Am. Chem. Soc., 80, 1977 (1958).
199. H. Neunhoffer, Chemistry of 1,2,3-Triazines, 1,2,4-Triazines, Tetrazines, and Pentazines, Wiley, New York (1978).
200. H. Schäfer and K. Gewald, J. Prakt. Chem., 322, 87 (1980).
201. V. L. Rusinov, A. Yu. Petrov, and I. Ya. Postovskii, Khim. Geterotsikl. Soedin., No. 9, 1283 (1980).
202. V. L. Rusinov, A. Yu. Petrov, and O. N. Chupakhin, in: Nucleophilic Reactions of Carbonyl Compounds [in Russian], Saratov (1982), p. 36.
203. W. E. Hahn and H. Zawadsk, Roczn. Chem., , 38, 557 (1964).
204. A. I. Dychenko and L. S. Pupko, Ukr. Khim. Zh., 40, 1220 (1974).
205. A. I. Dychenko, L. S. Pupko, and P. S. Pel'kis, Zh. Geterotsikl. Soedin., No. 9, 1290 (1975).