Synthesis of Nitrobenzazoles

Abstract A great deal of information on the methods of synthesis of nitrated benzo analogs – indazoles, benzimidazoles, benzoxazoles, benzisoxazoles, benzoxadiazoles, benzothiazoles, benzoisothiazoles, benzothiadiazoles, benzotriazoles, benzoselenazoles, benzoselenadiazoles – is systematized, summarized, and critically discussed. Major attention is paid to electrophilic nitration, a much used and convenient method for the preparation of nitrobenzazoles. The nitration of benzazoles is a complex process in which the experimental conditions can modify the product orientation. The existence of an annelated benzene ring in the benzazole molecule influences much of its ability for electrophilic substitution – all benzazoles are more easily nitrated than their five-membered analogs, and the nitro group is generally introduced into the arylene fragment of the molecule. Vicarious nucleophilic *C*-amination of benzazoles, practically, the single method of direct introduction of the amino group into nitro compounds is presented.

Introduction

The nitro derivatives of benzazoles have found wide applications in various branches of medicine, technology, and agriculture. For a long time they were used as radiosensitizers, anesthetics, anticancer medications, dyes, plasticizers, ionic liquids, pesticides, herbicides, and plant growth regulators. The nitrobenzazoles are convenient synthons and intermediates in organic synthesis. Benzotriazole, in particular, is a useful synthetic auxiliary: it is easily introduced, activates molecules toward numerous transformations, and can be removed readily at the end of the reaction sequence [1].

The syntheses of nitrobenzazoles have been critically discussed in our reviews [2]. Some representatives of nitrobenzazoles are described in Katritzky's works [3, 4] and reviews [6–8].

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The enormous amount of literature related to this topic made it necessary to exclude a series of references on earlier investigations and patents cited in the aforementioned reviews and monographs and also in more recent publications.

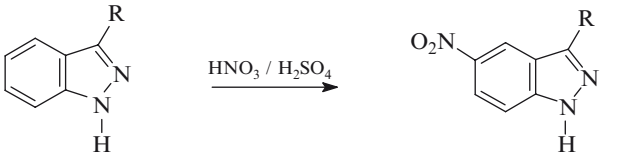
Some pioneering papers dealing with the synthesis of nitrated benzazoles have been included in the present chapter.

The most widespread and convenient method for the preparation of nitrobenzazoles is the reaction of nitration. Electrophilic substitution of azoles is a complex reaction in which the experimental conditions can modify the product orientation. The ability of azoles to electrophilic substitution is determined by the activity of reagents, the basicity of substrates, and the acidity of medium. This caused some uncertainty in interpreting the results and complicated comparison of the reactivity of various azoles among them. The situation has changed after Katritzky and Johnson [7] had reported the criteria allowing, with a sufficient degree of reliance, the establishment in what form (base or conjugative acid) the compound reacts. The information on the mechanism of nitration of azoles is basically borrowed from the extensive literature on the nitration of aromatic and heteroaromatic compounds [8]; therefore, it does not make sense to discuss this point in the review.

The existence of an annelated benzene ring in the benzazole molecule influences much its ability for electrophilic substitution. All benzazoles are more easily nitrated than their five-membered analogs, and the nitro group is generally introduced into the arylene fragment of the molecule.

Nitration of Benzazoles

Indazoles



R = H, CH_3, CH_2COOH, Cl, COOH, $COOCH_3$, CN

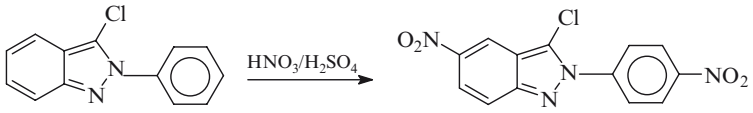
Scheme 2.1

Indazoles are nitrated, mainly into the position 5 by a mixture of sulfuric and nitric acids or just by nitric acid (Scheme 2.1) with formation of 5-nitroindazole derivatives that are a part of so-called universal nucleosides [9].

The presence of substituents mainly affects the direction of the process and not its rate. 1-Phenylindazole with 86% nitric acid gives a tetranitro derivative, which has one nitro group in the position 5; the second nitro group is in the *para*-position of the phenyl ring, with the position of the other two being not determined reasonably well [10]. If the nitration is performed by potassium nitrate in sulfuric acid, 1-(4-nitrophenyl)-5-nitroindazole is formed. Both the electron-donating and electron-withdrawing substituents at the indazole cycle C-3 atom direct the coming nitro

group to the position 5 in the nitration by nitric acid or by the mixture of sulfuric and nitric acids (Scheme 2.1) [10–16].

As mentioned in a patent [17], the nitration of 3-trifluoromethylindazole results in a mixture of 5-nitro- and 7-nitro-isomers. If the mixture of nitric and sulfuric acids is used as a nitrating agent, the formation of 3-methyl-7-nitroindazole as a by-product is observed [11]. Nitration of 3-chloro-2-phenylindazole with a mixture



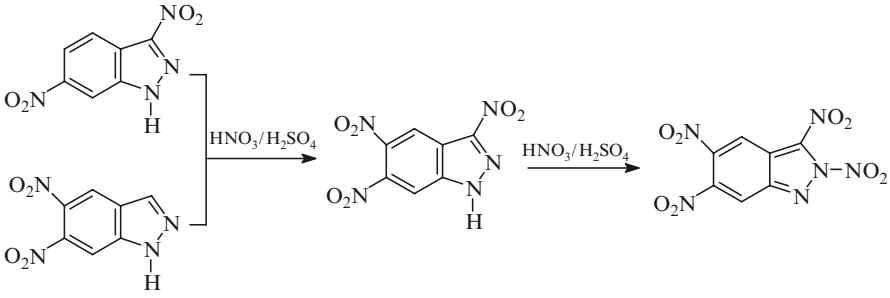
Scheme 2.2

of fuming nitric acid and concentrated sulfuric acid at 0°C gives 3-chloro-5-nitro-2-(4-nitrophenyl)indazole in yield 73% (Scheme 2.2) [18].

The nitration of 2-phenylindazole at 0°C with sulfuric–nitric acid mixture leads to 5-nitro-2-phenylindazole and 7-nitro-2-phenylindazole. These compounds have been identified using NMR spectroscopy [19]. In spite of the fact that the indazole positions 5 and 7 are most reactive with respect to electrophilic substitution [20] it is difficult to know beforehand the competition between the aromatic positions of the indazole ring (C-4, C-5, C-6, C-7) and the *N*-phenyl ring.

Electron-donating substituents in the indazole cycle positions 5 and 7 direct the coming nitro group to the position 4 [21, 22], and 6-acetylaminoindazole is nitrated to the position 7 [21]. It is known that 7-nitroindazoles are potent building blocks in divergent syntheses of bioactive compounds [23]. Under further nitration of mononitroindazoles the site of introduction of the second nitro group depends on both the position of the already present one and reaction conditions. For example, 5-nitroindazole is nitrated by the sulfuric–nitric acid mixture into 5,7-dinitro derivative, whereas in 6-nitroindazole the second nitro group enters into the position 5 [24]. After the nitration 7-nitroindazole forms 5,7-dinitro derivative [25].

The information about indazoles containing three or more nitro groups is rather scarce [26, 27]. Tetranitroindazole has been first assigned a wrong structure [26], but then it has been established to be 2,3,5,6-tetranitroindazole (Scheme 2.3) [27].



Scheme 2.3

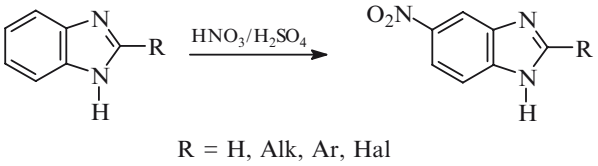
The formation of *N*-nitroazoles under the effect of sulfuric–nitric mixture is a rather seldom phenomenon [15, 27], since the *N*–NO_2 bond is unstable in acids. The most convenient way to *N*-nitroindazoles is nitration by acetyl nitrate [15, 27–37].

2-Nitroindazoles, the products of nitration with nitric acid in acetic anhydride, are easily rearranged to 3-nitro derivatives that make these isomers fairly accessible [28]. This method has been modified by Pozharskii [38] with a main goal to increase the yield of the reaction product. So 3-nitroindazole has been obtained without the intermediate 2-nitroindazole.

Kinetics and mechanism of nitration of indazoles with acetyl nitrate have not been specially investigated. In the sulfuric–nitric mixture indazoles are nitrated in the cation form [39].

Benzimidazoles

Benzimidazole is nitrated to the position 5(6) [40–44]. The same orientation is observed

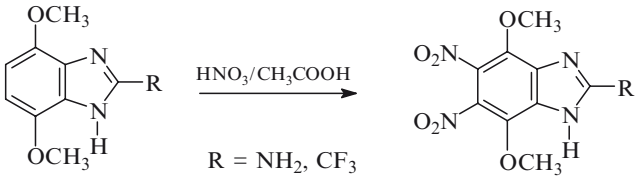


Scheme 2.4

in the nitration of different 2-substituted benzimidazoles (Scheme 2.4) [45–67].

In a boiling mixture of nitric (*d* 1.50) and concentrated sulfuric acids 2-chlorobenzimidazole gives 2-chloro-5,6-dinitrobenzimidazole in a 75–80% yield [67]. In analogous conditions, benzimidazole and 2-alkyl substituted benzimidazoles are also transformed into 5,6-dinitro derivatives; however, in this case simultaneous formation of 4,6-dinitro isomers, which can be separated by fractional crystallization, has been fixed [48, 68]. 5(6)-Nitro-2-heterylbenzimidazoles (thiazolyl-4-, furyl-4-, and pyrrolyl-4-) having antihelminthic activity were obtained by nitration with sulfuric–nitric mixture on cooling [69].

2-Trifluoromethyl- and 2-amino-4,7-dimetoxybenzimidazoles are nitrated to 5,6-dinitro derivatives already at 0°C (Scheme 2.5) [70].

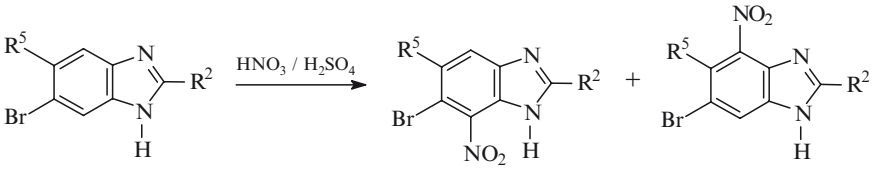


Scheme 2.5

The nitration of 5-nitrobenzimidazole under severe conditions gives two isomeric 5,6-dinitro- and 4,6(5,7)-dinitrobenzimidazoles. The structures of these products are identified only spectroscopically in the solution. The solid state structure of the major isomer 5,6-dinitrobenzimidazole has been determined by X-ray diffraction [71].

The nitration of 5-substituted benzimidazoles affords both mono- and dinitro derivatives. The two nitro groups occupy exclusively the positions 4 and 6 to form 5-substituted 4,6-dinitrobenzimidazoles [72–75]. It is interesting to note if in the nitration of 5-hydroxybenzimidazole the nitro group enters into the 4 position [74], whereas in the nitration of 5-chloro-, 5-ethyl-, and 5-ethoxybenzimidazole [73] and also 5-chloro- and 5-methyl-2-alkylbenzimidazoles [76, 77] it will occupy the 6 position. These data indicate that under the influence of electronic effects of the substituent in the position 5, the reactivity of C-4 and C-6 atoms of the benzimidazole ring is slightly equalized. That is why among the products of mononitration of 5-substituted benzimidazoles one can find 5-substituted 6-nitrobenzimidazoles [49, 75–80], 5-substituted 4-nitrobenzimidazoles [74, 75], and a mixture of these isomers [54, 75, 81, 82].

The nitration of 2-alkyl-5(6)-chloro(or methyl)-6(5)-halobenzimidazoles with excess nitric acid (~3 equivalents) in sulfuric acid leads to a mixture of 4-nitro- and 7-nitrobenzimidazoles except for 2-methyl-5,6-dibromobenzimidazole [76], as shown in Scheme 2.6. It is natural that 2-methyl-5,6-dibromobenzimidazole in the nitration under the same conditions gives 4(7)-nitro-2-methyl-5,6-dibromobenzimidazole in good yield.

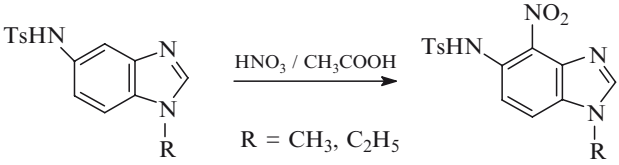


R^2 = Alk, R^5 = Hal, Me

Scheme 2.6

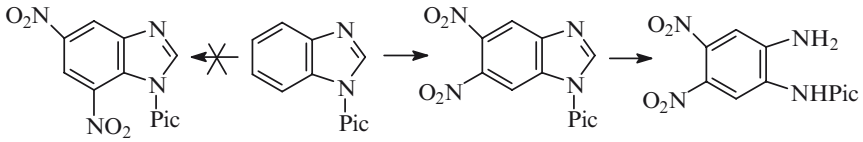
Preparation of 2,5(6)-dimethyl-4(7)-nitrobenzimidazole by nitration of 2,5(6)-dimethyl derivative has been reported in a patent [83], but there is no supporting evidence for the correctness of the assigned structures.

On nitration of 1-substituted benzimidazoles 5- and 6-nitro isomers [84–91] are formed. At the same time the nitration of 1-alkyl-5-tosylaminobenzimidazole with nitric acid in a solution of acetic acid leads to the formation of one isomer, the nitro group being involved in the position 4 (Scheme 2.7) [92].



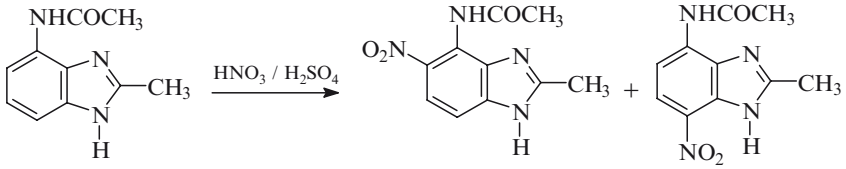
Scheme 2.7

The nitration of 1-picrylbenzimidazole with 100% nitric acid and 96% sulfuric acid gives, instead of the expected 5,7-dinitro derivative, the hydrolytically unstable 5,6-dinitro-1-picrylbenzimidazole that opens to the correspondent amine, as shown in Scheme 2.8 [93].



Scheme 2.8

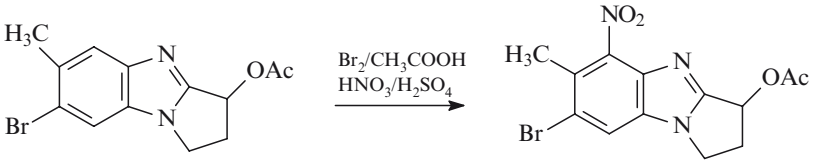
On nitration of 2-methyl-4(7)-acetylaminobenzimidazole two isomeric nitro products were obtained; the amount of 2-methyl-4(7)-acetylamino-7(4)-nitro isomer was twice as large (Scheme 2.9) [94].



Scheme 2.9

Prevailing formation of the 7-nitro derivative was observed in the nitration of 4-fluoro- [95] and 4-*tert*-butylbenzimidazole [96, 97]. When the benzimidazole ring has its 4 and 6 positions substituted, the nitration proceeds across the C-4 or C-7 atom [98–101].

In a medium of bromine in acetic acid and nitric–sulfuric mixture the benzimidazole derivatives are nitrated only to position 4 [102]. In this case the bromine is introduced into the position 5 or 6 (Scheme 2.10).



Scheme 2.10

Mechanism of the nitration of benzimidazoles has not been studied much, but there are weighty arguments to conclude that they are nitrated as conjugated acids [51, 103]. Kinetic studies of the nitration of benzimidazole and some of its 2-substituted derivatives have confirmed that the protonated form is involved in the process [104]. Recent results of quantum chemical studies of the nitration of benzazoles indicate the importance of the protonated benzimidazolium cations in the nitration process [43].

It has been noted that in the nitration of 2-phenylbenzimidazole, the rate of nitration into the benzimidazole 5 position is about three orders of magnitude higher than that of the phenyl ring [51].

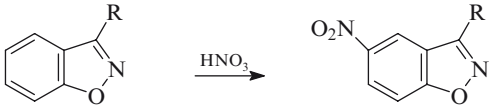
Benzimidazolone-2 and benzimidazolthione-2 derivatives are more prone to nitration [105, 106], and in this case the nitro group enters the position 5(6). It should be noted that depending on the reaction conditions, it is possible to obtain benzimidazolone dinitro, trinitro, or tetranitro derivatives [103, 107]. 5-Nitrobenzimidazolone-2 is nitrated with concentrated nitric acid on heating (80–90°C) only to the position 6 to give 5,6-dinitrobenzimidazolone-2 [108].

In the reaction of nitronium tetrafluoroborate with 1-aminobenzimidazole the nitro group enters the side chain with the formation of *N*-nitroimides [109]. In some cases the nitration of benzimidazoles with acetylnitrate leads to 1-nitrobenzimidazoles [110].

Some examples of the nitration of benzimidazole derivatives have been reported [110–114].

Benzisoxazoles, Benzoxazoles, and Benzoxadiazoles

1,2-Benzisoxazole and its 3-substituted derivatives are nitrated into the position 5 (Scheme 2.11) [115–125].



R = H, Alk, COOR'

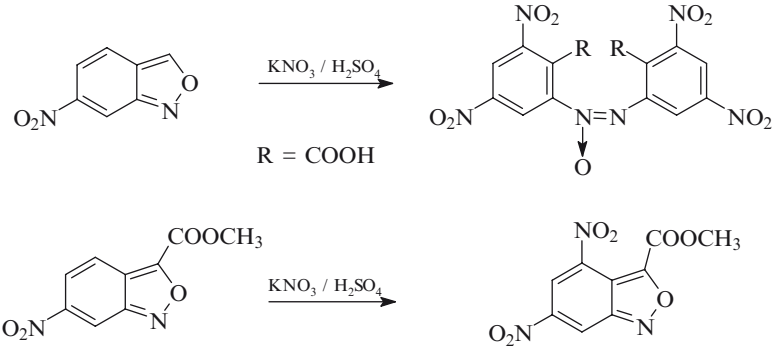
Scheme 2.11

The nature of substituent in the arylene fragment significantly influences the nitration direction. For example, 3,5-dialkyl-1,2-benzisoxazoles are nitrated into the position 4 (the data about the formation of 3,5-dimethyl-7-nitro-1,2-benzisoxazole presented in [115] turned out to be wrong [119], whereas 3-alkyl-5-nitro derivatives occupy the position 7 [119]). The nitration of 7-methoxy-2-phenylbenzisoxazole affords 7-methoxy-2-phenyl-4-nitro derivative [126].

The mechanism of the nitration of benzisoxazoles in sulfuric–nitric acid mixture has been studied with 3-methyl-1,2-benzisoxazole [121]. It has been found that at a sulfuric acid concentration of about 80–90% the substrate reacts as a free base, and at a higher concentration the conjugated acid undergoes nitration. It is worth mentioning that in 1,2-benzisoxazole and its 3-methyl derivative the higher electron density is concentrated on the C-7 atom and in the case of charge-controlled reactions the nitration would lead to 7-nitro isomers. Since 5-nitro derivatives are formed, the process of nitration seems to be of orbital-controlled character [121].

The nitration of 2,1-benzisoxazoles (anthranils) and their thioanalogs is poorly understood. Unsubstituted anthranil and its 3-methyl and 3-chloro derivatives are nitrated, generally, on the C-5 atom (in the first two cases, along with the main product small amounts of 7-nitro isomer were obtained) [127, 128]. When heated, 6-chloro-2,1-benzoxazole (6-chloranthranil) forms only 7-nitro derivative [129]. The nature of substituent significantly influences the site of the nitro group introduction. For example, on heating 5-chloroanthranil forms 5-chloro-4-nitroanthranil, but its 3-phenyl derivative is nitrated into the position 7 (along with the nitro group entering into the phenyl ring) [130].

It was impossible to introduce the second nitro group into 6-nitroanthranil because of the heterocycle ring opening, as shown in Scheme 2.12; however, 3-carbomethoxy-6-nitro-2,1-benzisoxazole is more easily nitrated to 4,6-dinitro derivative [130].

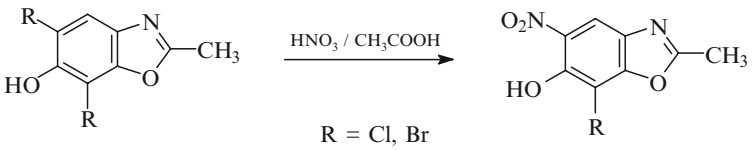


Scheme 2.12

In benzoxazoles and their 2-substituted derivatives the nitro group is presumably introduced into the position 6 [131–135]. In the nitration of 2-methylbenzoxazole a mixture of 80% of 6-nitro- and 20% of 5-nitro isomer was isolated. 2-Phenylbenzoxazole is first nitrated to the position 6 [136, 137]. The nitration of benzoxazolones-2 and benzoxazolthiones-2 proceeds in an analogous way [138–141].

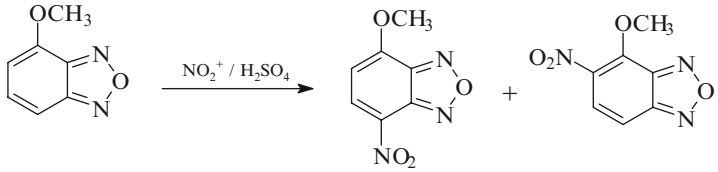
The reaction of cooled nitric acid with benzoxazole results in the formation of a mixture of 2-hydroxy-4-nitro- and 2-hydroxy-5-nitroformylanilines. On heating the same reaction gives a mixture of 5- and 6-nitrobenzoxazoles – the latter being prevailing [131]. Here, a question arises whether the formation of nitrohydroxyformylaniline results from the hydrolysis of the nitrobenzoxazole formed or it is due to the nitration of hydroxyformylaniline (the product of benzoxazole hydrolysis). The authors have shown the nitration precedes to the hydrolysis [131]. If the position 6 in benzoxazole is occupied, the nitration goes into the position 5 [142]. In the same work an example of nitrolysis (substituting nitration, *ipso*-nitration) of 2-methyl-5,7-dihalogeno-6-hydroxybenzoxazoles is given (Scheme 2.13).

Substituted benzoxazoles are also nitrated with nitric–sulfuric mixture into the 6 position, if it is vacant [143, 144]. In earlier publications it has been stated that benzofurazans (2,1,3-benzoxadiazoles) are nitrated exclusively to the 4(7) position



Scheme 2.13

[145–147]. If the 4 and 7 positions are occupied, as in 4,7-dichloro-2,1,3-benzoxadiazoles, for example, the nitration is impossible. At the same time, 4,6-dichloro-7-nitrobenzofurazan was obtained in good yield from 4,6-dichlorobenzofurazan [148]. Later it has been shown that in the presence of strong electron-donating substituents (like OCH_3) and along with nitration to the position 7 the addition of the nitro group to the C-5 atom takes place (Scheme 2.14) [149].



Scheme 2.14

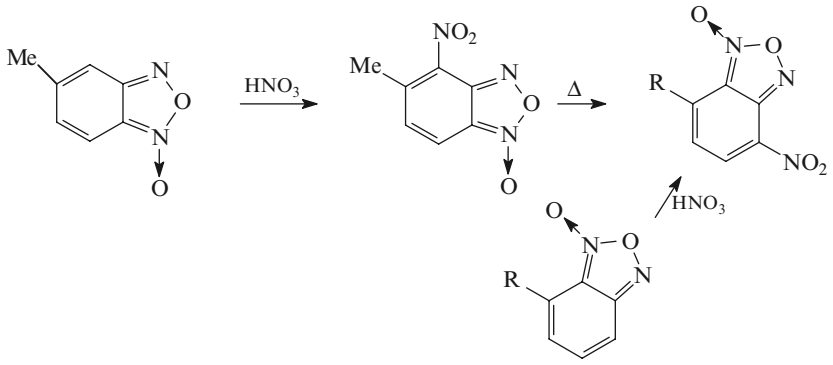
As expected, strong electron-deficient substituents in the position 5 orient the incoming nitro group exclusively to the position 7 [150, 151]. 7-Nitrobenzofurazans possess fluorescent properties and may be useful as biochemical fluorescent probes [152]. Some examples of obtaining dinitrobenzofurazans by nitration are described in references [153, 154].

The benzofuroxan phenylene ring is subjected to electrophilic substitution, in particular, nitration reaction. If the nitro group is introduced into the position neighboring to the heterocycle, the nitro compound formed undergoes the so-called Boulton–Katritzky rearrangement [155–161].

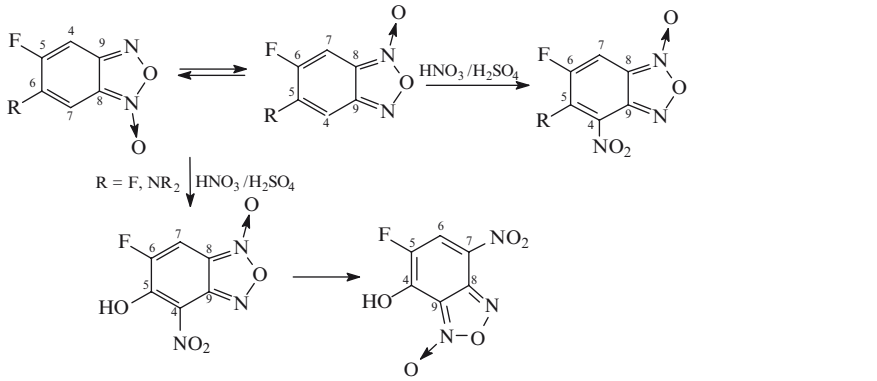
The nitration of 5-methylbenzofuroxan results in a 4-nitro derivative, which on heating is transformed to a more stable 7-methyl isomer according to the Boulton–Katritzky rearrangement. As shown in Scheme 2.15, the latter compound is obtained by direct nitration of 4-methylbenzofuroxan [159].

Similarly, 5-chloro-4,6-dinitrobenzofuroxan prepared by the nitration of 5-chlorobenzofuroxan by HNO_3/H_2SO_4, 0→21°C [162] undergoes the Boulton–Katritzky rearrangement (28°C, 51 h, $CHCl_3$) to give 7-chloro-4,6-dinitrobenzofuroxan.

It has been pointed out [155] that in the presence of fluorine atom in the position 5 in 4-nitrobenzofuroxan no Boulton–Katritzky rearrangement occurs. Later it has been established [161] that fluoro-containing benzofuroxans are fairly easily nitrated; however, not all nitration products are involved in the Boulton–Katritzky rearrangement. 5,6-Difluorobenzofuroxan and 5(6)-amino substituted 6(5)-fluorobenzofuroxans are nitrated with HNO_3 (*d* 1.54) and H_2SO_4 acids on cooling to form 4-nitro-5-hydroxy-6-fluorobenzofuroxan (Scheme 2.16) [161].



Scheme 2.15



R = F, $N(CH_3)_2$, morpholino, thiomorpholin-4-yl, pyrrolidin-1-yl, OCH_3, OC_2H_5, tetrahydrofuran-2-yl methoxy

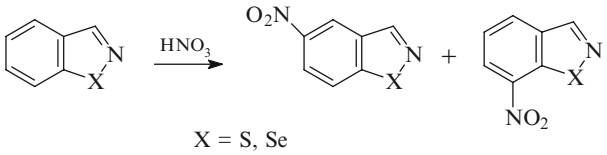
Scheme 2.16

Under nitration conditions the substituted fluorine (or the amine group) in the position 5 is easily hydrolyzed to hydroxy group. 4-Nitro-5-hydroxy-6-fluorobenzofuroxan, on dissolving in a polar solvent (DMSO), partly transforms to 4-hydroxy-5-fluoro-7-nitrobenzofuroxan as a result of the Boulton–Katritzky rearrangement (Scheme 2.16) [161]. Under nitration of 5(6)-alkoxy-6(5)-fluorobenzofuroxans the corresponding 4-nitrobenzofuroxans were obtained. In this reaction the C-4 atom in the *ortho*-position to the electron-donating substituent and remote from the *N*-oxide group is also the center of electrophilic attack. In this case, however, no products of the Boulton–Katritzky rearrangement are formed.

4,6-Dichlorobenzofuroxan is nitrated by HNO_3 and oleum 30% to form 4,6-dichloro-5,7-dinitrobenzofuroxan, one of the most perspective precursors of explosive compounds [162].

Benzisothiazoles, Benzothiazoles, and Benzothiadiazoles

Like 1,2-benzoselenazole [163], 1,2-benzothiazole [164–166] on heating forms a mixture of 5-nitro- and 7-nitro isomers (Scheme 2.17).



Scheme 2.17

The introduction of substituents into the position 3 does not change the reaction course [165, 167–169]. 4-Amino-7-nitrobenzisothiazole in the sulfuric–nitric mixture forms 5,7-dinitro derivative in low yield [170]. 4-Chloro-7-nitro-1,2-benzisothiazole was obtained as a result of the nitration of 4-chloro-1,2-benzisothiazole [171, 172]. 5-Hydroxy-1,2-benzothiazole is nitrated to the position 4, and in case of 5-hydroxy-4,6-dibromo-1,2-benzisothiazole a substitutive nitration to form 5-hydroxy-6-bromo-4-nitro isomer occurs [173].

The main product of the nitration of 2,1-benzisothiazole (thioanthranil) is 5-nitro-2,1-benzisothiazole (57%); however, alongside significant amounts of other isomers such as 7-nitro- (26%) and 4-nitro-2,1-benzisothiazole (17%) are formed [174]. The nitration of several other substituted thioanthranils has also been carried out [128, 174–176].

6-Nitrobenzothiazole is the main product of the nitration of benzothiazoles [177–183]. In several works it has been noted that along with this product some other hardly separable isomers are formed. Ward and Poshe [177] have developed a method to separate mixtures of isomers and showed that on nitration four isomers can be formed (Table 2.1).

2-Substituted derivatives of benzothiazole are also nitrated principally into the position 6 [134, 184–192]. Nevertheless, nitration of 2-aryl-4,7-dimethoxy benzothiazoles results in a mixture of 5- and 6-nitrobenzothiazoles [193]. In 2-phenyl substituted benzothiazoles the nitro group first enters into the benzothiazole cycle [178, 187, 194]. Like 2-aminothiazoles, 2-aminobenzothiazoles first form with the sulfuric–nitric mixture nitramines, which later are rearranged to 2-amino-6-nitrobenzothiazoles. If the benzothiazole position 6 is already occupied by a rather strong electron-withdrawing substituent (NO_2, RSO_2), the nitro group enters into

Table 1 Isomers ratio in the nitration of benzothiazole with sulfuric–nitric mixture

		Yield of isomeric nitrobenzothiazoles (%)			
t (°C)	Total yield (%)	4-NO_2	5-NO_2	6-NO_2	7-NO_2
10±2	83.0	22.6	6.4	49.6	21.3
35±2	91.6	21.4	8.5	50.1	20.0

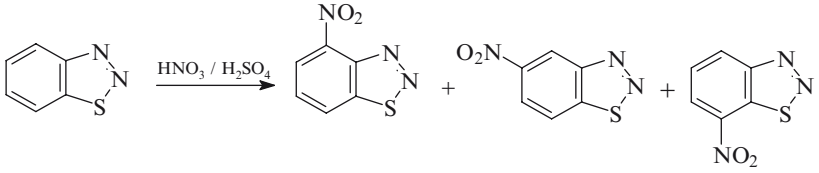
the position 4. Strong electron-donating substituents at the C-6 atom (NH_2, OCH_3) orient the incoming nitro group mainly to the position 7 [194–197]. Nitration of other benzothiazole derivatives has also been carried out [134, 198–202].

As a result of the nitration of benzothiazolones-2 [136, 203, 204] and benzothiazolylthiones-2 [205, 206] with the sulfuric–nitric mixture 6-nitro isomers are obtained.

The nitration of benzothiazoles with ethyl nitrate [207] is analogous to that with the sulfuric–nitric mixture.

Unlike 1,2,3-benzoxadiazoles the existence of which is open to question [208–210], 1,2,3-benzothiadiazoles are well known and their nitration has been described in the literature. On nitration of 1,2,3-benzothiadiazoles with sulfuric–nitric mixture Overberger et al. [211] have obtained 4-nitro-1,2,3-benzothiadiazole.

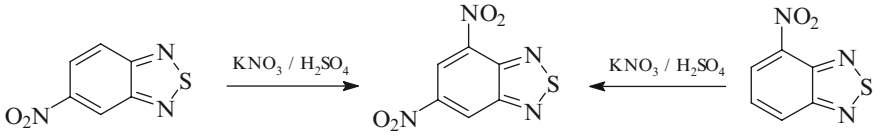
Freis and Reitz, using potassium nitrate in sulfuric acid on heating, have obtained two mononitrated products and assigned to them the structures of 4- and 7-nitro isomers [212]. Later, this structure has been proved by a secondary synthesis [213], and the other isomer turned out to be 5-nitro-1,2,3-benzothiadiazole [214, 215]. On a more careful study all three isomers were found among the reaction products, as shown in Scheme 2.18 [216].



Scheme 2.18

Substituted 1,2,3-benzothiadiazoles are nitrated to the position 5 or 7 if they are vacant [197, 217–219]. The data [218] on the synthesis of 4-nitro-substituted 1,2,3-benzothiadiazoles need to be checked.

Like benzofurazan, 2,1,3-benzothiadiazole is also nitrated to the position 4(7) [220, 221]. If there are electron-donating substituents (CH_3, OH, OCH_3) at the C-5 atom, 4-nitro derivatives are readily obtained in high yield [222–229]. The electron-withdrawing substituents (nitro group) at the same carbon atom direct the incoming nitro group to the 7(4) position [230]. So, on heating 5-nitro- and 7-nitro-2,1,3-benzothiadiazoles turn into 5,7-dinitro-2,1,3-benzothiadiazole (Scheme 2.19).



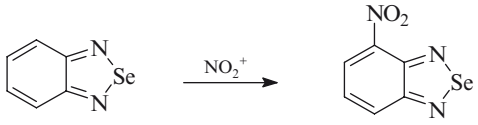
Scheme 2.19

Electron-donating substituents at the C-4 atom direct the incoming nitro group to the position 5 or 7; however, the amount of 7-nitro isomer is higher than that of 4-nitro isomer [222–234]. The direction of the nitration of di- and tri-substituted 2,1,3-benzothiadiazoles is determined by the position and electron nature of substituents [223, 227, 229, 230, 232, 235–239]. *Ipso*-nitration of 4,7-dibromo-2,1,3-benzothiadiazole to form 4-bromo-7-nitroderivative has been reported [235].

Benzoselenazoles and Benzoselenodiazoles

Benzoselenazoles and their derivatives are also nitrated at the position 6 [240, 241]. The nitration can be accompanied by the oxidation of the azole ring, and 6-nitrobenzoselenazolone-2 can be isolated as a by-product.

The nitration of 2,1,3-benzoselenodiazoles proceeds in the same way as with their thio analogs. For example, 2,1,3-benzoselenodiazole, in the sulfuric–nitric mixture, is transformed into a 4-nitro derivative with a yield of 90–98% (Scheme 2.20) [223, 230, 242–245].



Scheme 2.20

From the preparative point of view, especially when working with small amounts of the substrate, it is reasonable to use nitration with a mixture of sodium nitrate and sulfuric acid [245, 246]. This method allows simultaneous introduction of two nitro groups into 4 and 7 positions of the annelated benzene ring. Under nitration of 5,6-disubstituted 2,1,3-benzothia- and 2,1,3-benzoselenodiazoles a regular enhancement of deactivating effect of the substituent on the reactivity of 2,1,3-benzothia- and 2,1,3-benzoselenodiazole is observed (in the following order: $CH_3 < Cl < NO_2$). Under these conditions neither 5,6-dinitro-2,1,3-benzoselenodiazole or its thio analog undergo nitration [246].

The direction of substitution upon nitration of 2,1,3-benzoselenodiazole derivatives [230, 247–249] is the same as that for their thio analogs.

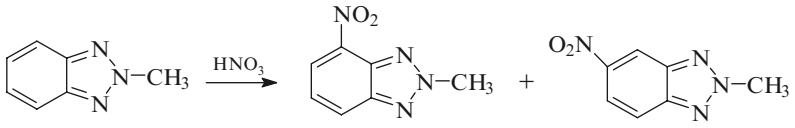
Benzotriazoles

On nitration of unsubstituted benzotriazole the nitro group enters into the position 4(7) [43, 250–254]. 6(5)-Methyl-5,7(4,6)-dinitrobenzotriazole has been synthesized by nitration of 6(5)-methyl-7(4)-nitrobenzotriazole under thermal conditions

and by novel mode – microwave irradiation [255]. Advantages of the microwave irradiation method are shown.

Earlier the nitration of 1-methylbenzotriazole was considered to lead to 7-nitro isomer [250, 252], but later the formation of 1-methyl-4-nitrobenzotriazole was proved [256]. Other 1-substituted benzotriazoles are also nitrated to the position 4 [257–261]. Arguments of Feldman and Usovskii in favor of their synthesis of 5-alkoxy-6-nitrobenzotriazoles turned out to be incorrect [262]; actually, the authors obtained 4-nitro isomers [263]. On boiling in the mixture of sulfuric and nitric acids 1-picrylbenzotriazole is nitrated into 5,7-dinitro-1-picrylbenzotriazole [264]. It is interesting to note that 6-nitro-1-picrylbenzotriazole in nitric acid gives 5,6-dinitro derivative, whereas in sulfuric–nitric mixture 5,6,7-trinitro derivative is formed. In fact, we can prove the formation of the latter only indirectly, since one of the nitro groups is easily substituted by the methoxy group on dissolving the reaction product in methanol [264]. At the same time 1-(2,4-dinitrophenyl)-5-nitrobenzotriazole was obtained from 1-(2,4-dinitrophenyl)benzotriazole with sulfuric–nitric mixture [265]. The main product of the nitration of 5-R-benzotriazole is 5-R-4-nitrobenzotriazole [250, 255, 266, 267].

Previously it was believed that only one 4-nitro isomer was obtained on nitration of 2-methylbenzotriazole [268]; however, later it was shown that the authors dealt with a mixture of 4- and 5-nitro isomers (Scheme 2.21) [269].



Scheme 2.21

Under nitration, benzotriazolyl-2 acetic acid gave only one 4-nitro isomer [270]. The same results were achieved with the nitration of 2-(4-nitrophenyl)benzotriazole [271]. Structure of the nitration products of some benzotriazoles has not been determined till the present time [272].

The use of acetyl nitrate in place of sulfuric–nitric mixture as a nitrating agent leads to 1-nitro derivatives [28]. These compounds have also been obtained by the nitration of 1-chlorobenzotriazole with a silver nitrate complex with trimethylphosphite [273].

1-Hydroxybenzotriazole is nitrated with nitric acid in glacial acetic acid to give 6-nitro derivative, whereas the use of sulfuric–nitric mixture does not lead to positive results [274]. 1- and 2-Aminobenzotriazoles react with nitronium boron fluoride to form nitroimides isolated as alkali metal salts, involving no nitro group in the phenylene fragment [109].

Quantum chemical studies (MP2/cc-pVDZ treatment) of the reactivity of benzazoles indicate the preferred nitration of benzotriazoles and their protonated cations into the 4- and/or 7-position that is in good agreement with the experiment [43].

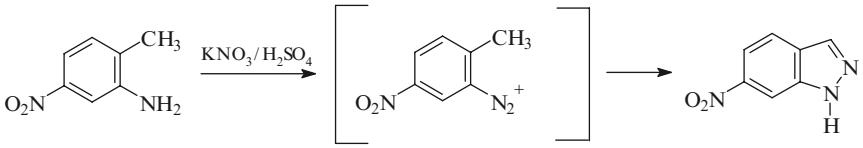
So-called *Kyodai* nitration – a novel methodology of nitration with nitrogen dioxide and ozone – has been applied to several benzimidazoles with formation of 1-nitrobenzimidazoles and following conversion to 1-nitrobenzotriazoles [275].

The nitration of benzotriazole *N*-oxide with dilute nitric acid gives the 7-nitro derivatives, whereas nitration with a mixture of nitric and acetic acids leads to 5-nitro- and 7-nitro isomers in a ratio of 1:9 [276].

Synthesis of Nitrobenzazoles via Heterocyclization

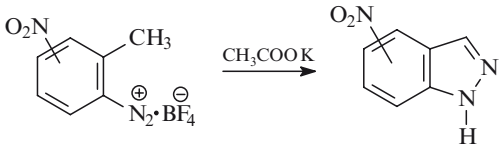
Nitroindazoles

The reactions of heterocyclization also have a wide preparative usage in the synthesis of nitrobenzazoles. Here, the nitro group first enters into one of the fragments from which the heterocyclic system is being built. In this case the presence of the nitro group often influences much of the course of the process. The diazotization of *ortho*-toluidine results in the formation of indazole in a yield not more than 5%. At the same time, 4-nitro-2-aminotoluene under the same conditions transforms to 6-nitroindazole in high yield, as shown in Scheme 2.22 [277–279].



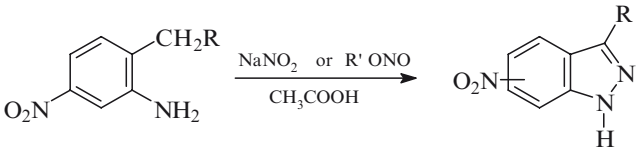
Scheme 2.22

4-Nitro- [280], 5-nitro- [277, 278, 281], and 7-nitroindazoles [278, 280, 282–285] are obtained in an analogous manner. The diazonium salt, obtained from 2-amino-6-nitro-*meta*-xylole, gives a mixture of 7-methyl-4-nitro- and 7-methyl-6-nitroindazole. It should be noted that the reaction of diazotization of *ortho*-toluidines, having other substituents apart from the nitro group, is often used to obtain different nitroindazoles [11, 18–22, 24, 25, 279, 280, 286, 287]. An original method of the synthesis of nitroindazoles involves the reaction of *ortho*-tolyldiazonium tetrafluoroborate with potassium acetate in the presence of crown ethers (18-crown-6) (Scheme 2.23) [288–290]. The reaction of cyclization has a high rate at room temperature (yield 60–90%).



Scheme 2.23

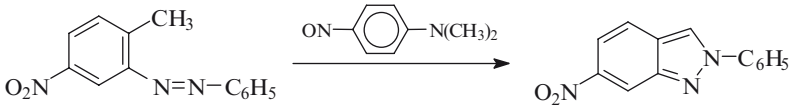
The diazotization of 2-alkylaminoanilines containing the nitro group in the phenyl ring leads to 3-substituted indazoles (Scheme 2.24) [11, 17, 282, 291, 292].



R = CH_3, CF_3, R' = Alk

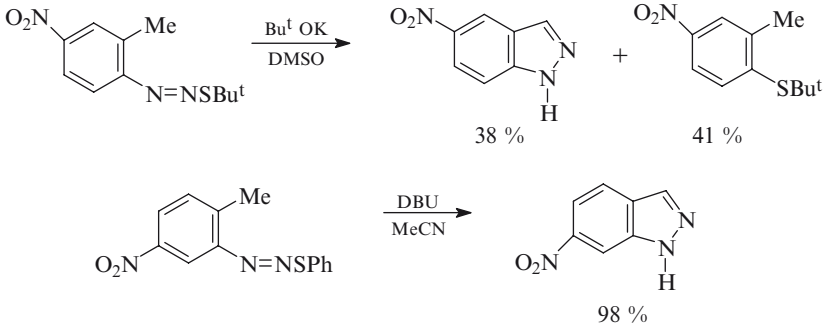
Scheme 2.24

Diazoamino compounds are formed, and sometimes they can be obtained as intermediates [282]. In some cases nitroindazoles as by-products are determined on diazonation of nonnitrated *ortho*-toluidines with isoalkylnitrite [293]. 2-Phenylazo-4-nitrotoluene gives 2-phenyl-6-nitroindazole on boiling with *para*-nitrosodimethylaminobenzene (Scheme 2.25) [294].



Scheme 2.25

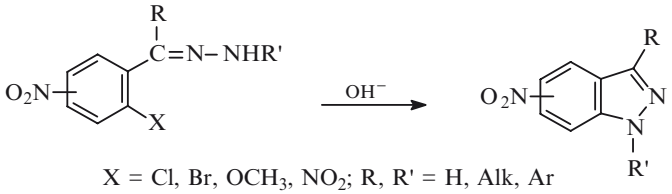
In this case the activation of the methyl group by the nitro group is a necessary reaction condition. Moreover, the nitro group has to be in the *ortho*- or *para*-position to the methyl group [294, 295]. If it is in the *meta*-position, no indazole is formed. This is in good agreement with larger yields of 6-nitroindazole in comparison with the ones of 5-nitroindazole (Scheme 2.26) [296].



Scheme 2.26

It means that more drastic reaction conditions are necessary for the cyclization with a methyl group in the *meta*-position.

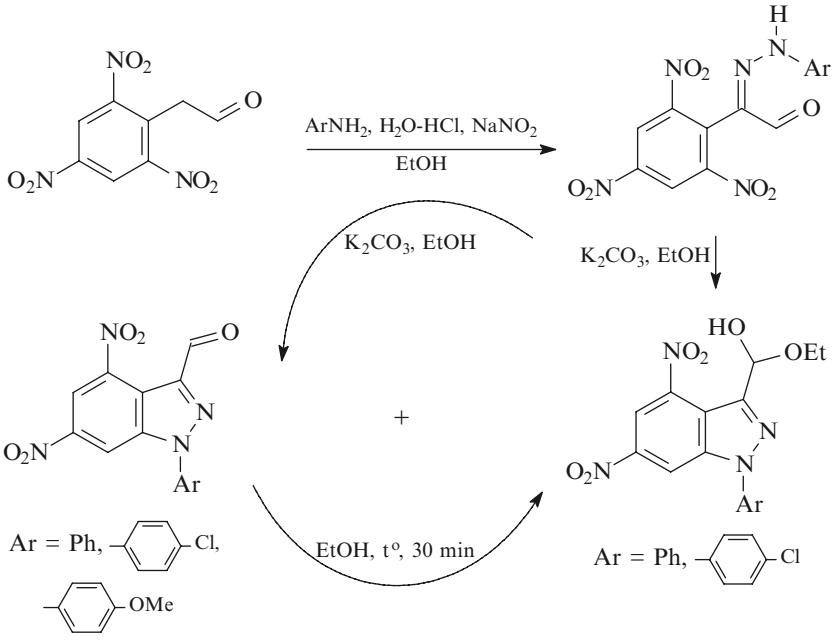
Another widespread synthetic route to nitroindazoles is the reaction of intermolecular cyclization of *ortho*-substituted arylhydrazones, as shown in Scheme 2.27 [10, 297–304].



Scheme 2.27

Besides, in this case the aromatic ring nitro group influences the reaction pathway much. 2-Bromobenzophenone, when heated up to 200°C with hydrazinium hydrate, gives 3-phenylindazole in a very small yield, whereas bromo-5-nitrobenzophenone reacts at 140°C to form 5-nitro-3-phenylindazole in a yield of 65% [298]. In analogous conditions the corresponding indazole is obtained from 2-bromo-3,5-dinitrobenzophenone in high yield [298].

1-Aryl-4,6-dinitroindazoles are obtained by treatment with alkaline metal carbonates of the corresponding hydrazones [302–304]. The latter are formed from picryl acetal aldehydes with aryldiazonium salts. Scheme 2.28 demonstrates that

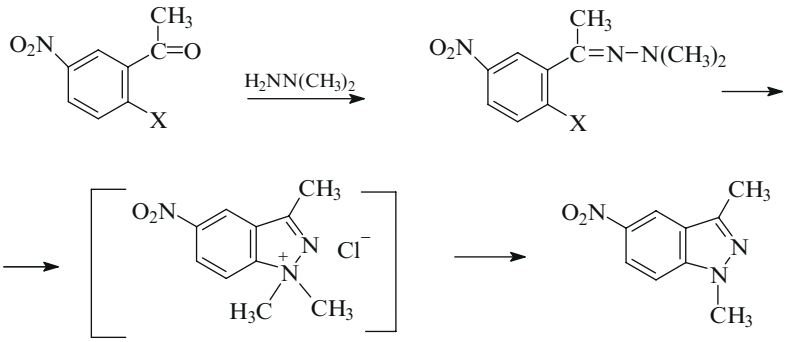


Scheme 2.28

the cyclization of hydrazones occurs due to intramolecular nucleophilic substitution of the nitro group.

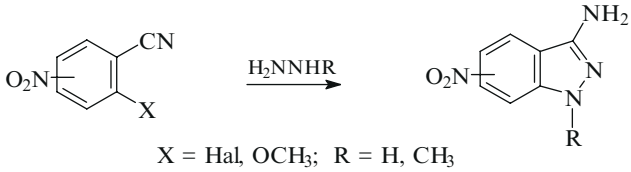
Stable semiacetals can be formed in parallel with dinitroformylindazoles in the absence of electron-donating groups such as 4-MeO-C_6H_4, for example, in the *N*-aryl substituent. Dinitroformylindazoles readily transform to the corresponding semiacetals when boiled in ethanol for 30 min. At the same time, on heating of crystalline semiacetal (Ar = Ph) in the air (80°C, 8 h) an ethanol molecule is abstracted and the corresponding dinitroformyl indazole is regenerated [302, 303].

The pathway of the reaction of 2-chloro-5-nitrobenzophenone with excess *N,N*-dimethylhydrazine is rather interesting (Scheme 2.29). In this case 1,3-dimethyl-5-nitroindazole is formed fast and in high yield [305].



Scheme 2.29

When boiled with hydrazine hydrate, the esters of nitrated *ortho*-halogenobenzene acids transform to corresponding nitroindazolones-3 [306, 307]. 2-Halogeno- or 2-methoxy-X-nitrobenzonitriles are also involved in an analogous reaction (Scheme 2.30) [308–314].

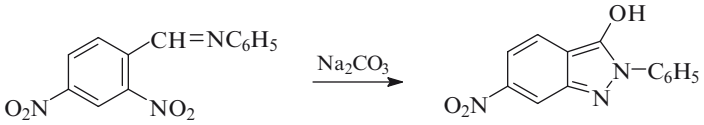


Scheme 2.30

It should be noted that in earlier publications the reaction products were wrongly assigned a structure of 2-cyano-4-nitrophenylhydrazine [308–310] (see [312]).

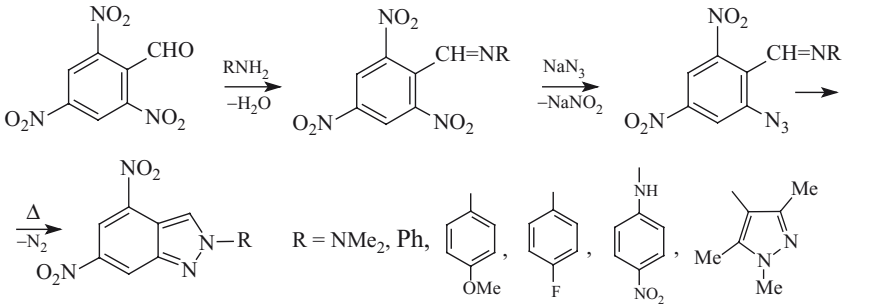
To simplify the synthetic technology of 3-amino-5-nitroindazole and to improve the target product quality it is reasonable to use 2-cyano-4-nitroaniline. The latter is subjected to diazotization, and the azo compound thus formed is reduced with simultaneous closure of the indazole cycle with sulfur dioxide in 5–15% sulfuric acid [315].

There are some ways of preparing nitroindazoles by the reactions of heterocyclization and recyclization. For example, if some Schiff's bases containing a nitro group in the *ortho*-position to the methylene fragment are boiled in an ethanolic sodium carbonate solution, nitro derivatives of indazole are formed (Scheme 2.31) [285, 316–318].



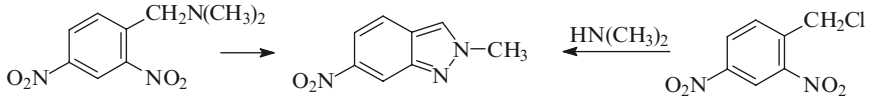
Scheme 2.31

Chemical utilization of explosive 2,4,6-trinitrotoluene (TNT) can lead to 4,6-dinitroindazoles. An original method of preparing 2-substituted 4,6-dinitroindazole involves the formation of *C*-(2,4,6-trinitrophenyl)-*N*-R-azomethines from TNT or the product of its transformation, 2,4,6-trinitrobenzaldehyde with further regiospecific substitution of the nitro group under the action of NaN_3 [319]. Thermolysis of the azides in ethylene glycol at 150–180°C gives the corresponding 4,6-dinitroindazole derivatives in high yields (Scheme 2.32) [319].



Scheme 2.32

An interesting event of intermolecular cyclization has been found on nitrating 4-nitrobenzyldimethylaniline [320]. On standing, the 2,4-dinitro-*N,N*-dimethylbenzylamine formed spontaneously transforms to 2-methyl-6-nitroindazole, which is also obtained in the reaction of dimethylamine with 2,4-dinitrobenzylchloride (Scheme 2.33).

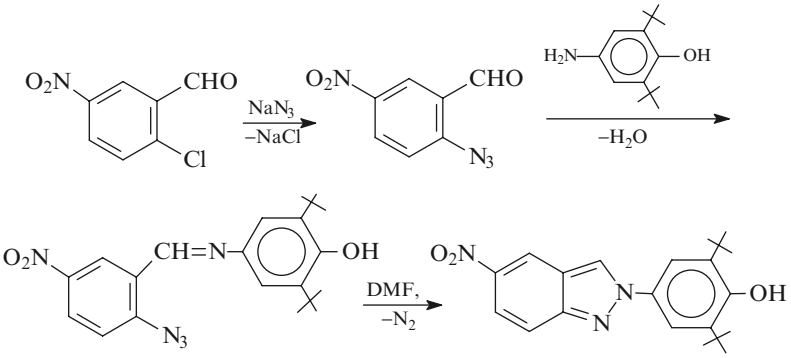


Scheme 2.33

Previously, 2-methyl-6-nitroindazole *N*-oxide was suggested to be the reaction intermediate. However, it was not possible to determine its formation in the

experimental conditions by means of IR and NMR spectroscopy [321]. That is why a more probable reaction pathway seems to be as follows. The reaction is catalyzed with bases and slowed down with acids that prove the suggested Scheme [321].

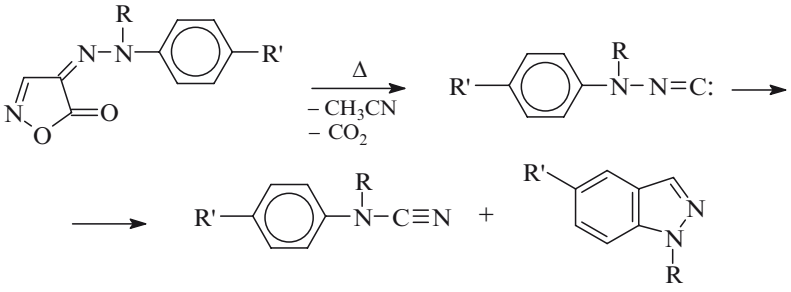
For the synthesis of antioxidants containing fragments of sterically hindered phenol and indazole a method involving thermal decomposition of 2-azidobenzylidenamines to 1,2-dichloro- or 1,2,4-trichlorobenzene and resulting in 2-substituted indazoles was used [321]. So, as seen from Scheme 2.34, 2-chloro-5-nitrobenzaldehyde gives the corresponding azidoaldehyde and then 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-nitroindazole.



Scheme 2.34

Intermediate azomethine could not be isolated. Heating of *N*-(2-azido-5-nitrobenzyliden)aniline in dimethylformamide affords to 2-phenyl-5-nitroindazole, the structure of which has been confirmed by X-ray diffraction [322].

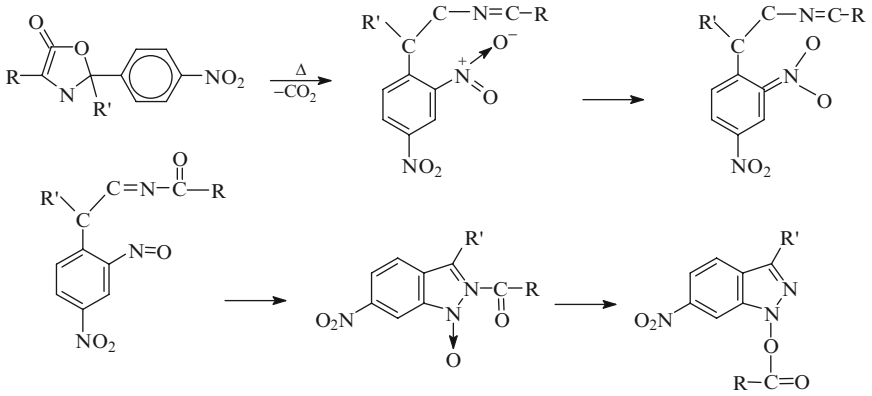
The pyrolysis of 4-arylhydrazono-3-methylisoxazolone-5 forms isocyanoamines, which undergo rearrangement to cyanoamides and corresponding indazoles (Scheme 2.35). Among other compounds 5-nitroindazole was obtained in an analogous way [323].



Scheme 2.35

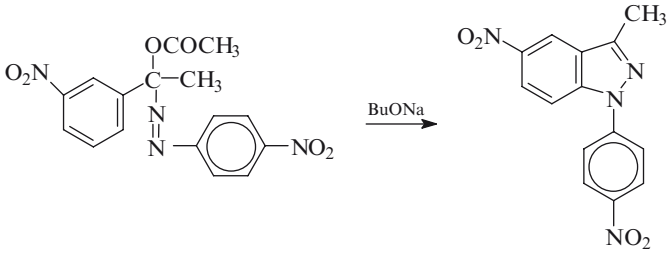
2-(2,4-Dinitrophenyl)-3-oxazolinones-5 behave in a similar way on heating: the elimination of carbon dioxide leads to (2,4-dinitrophenyl)-nitrylimide from which (2-nitrozo-4-nitrophenyl)-*N*-acylimine is formed after intermolecular oxygen

migration. The *N*-acylimine undergoes cyclization to unstable 2-acetyl-6-nitroindazole *N*-oxide with a fast migration of the acyl group to 3-substituted 1-acyloxy-6-nitroindazole (Scheme 2.36) [324].



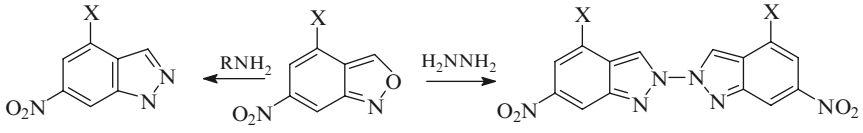
Scheme 2.36

α-Methyl-3-nitro-4-nitrophenylazobenzylacetate on heating with sodium butoxide transforms to 3-methyl-5-nitro-1-(4-nitrophenyl)indazole (Scheme 2.37), but the yield of the final product is 15% in this case [300].



Scheme 2.37

6-Nitroanthranils react with primary amines or with phenylhydrazine to form 2-substituted 6-nitroindazoles [325, 326]. 6,6′-Dinitro-2,2′-bis-indazolyls were obtained in the reaction with hydrazine (Scheme 2.38) [325, 326].

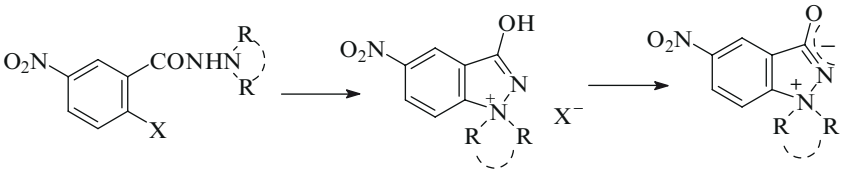


X = H, Cl, Br, I; R = C_6H_5, C_6H_5NH

Scheme 2.38

Nitroindazolones are prepared on heating from the corresponding 2-bromo-3-nitrobenzoates with hydrazine hydrate [327].

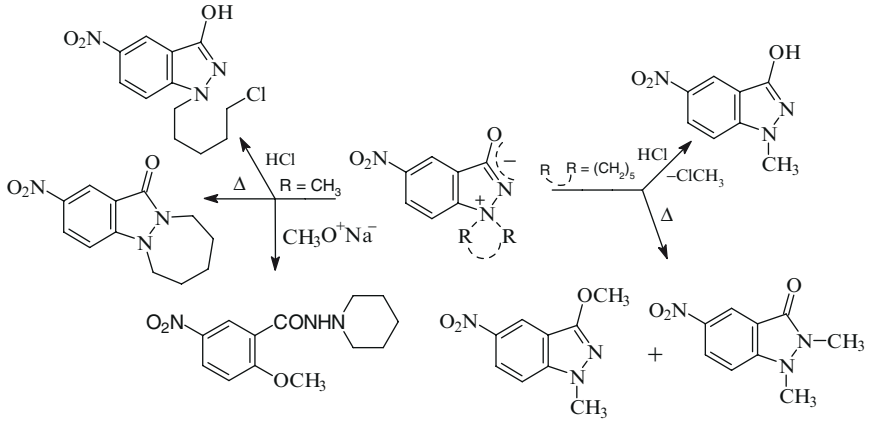
Stable nitroindazolyl-3 oxides (betaines) were obtained in 80–90% yield from the corresponding 2-halogenobenzohydrazides (Scheme 2.39); moreover, from chlorobenzohydrazides betaines are formed in more rigorous conditions [328].



X = F, Cl; R = CH_3, C_2H_5

Scheme 2.39

The treatment of betaines with concentrated sulfuric acid leads to the corresponding derivatives of 5-nitroindazole (products of alkylhalogenides elimination). Heating of betaines results in other nitroindazoles: a product of Steven's rearrangement or a mixture of *N*,*O*- and *N*,*N*-alkyl shift products, as shown in Scheme 2.40 [328].



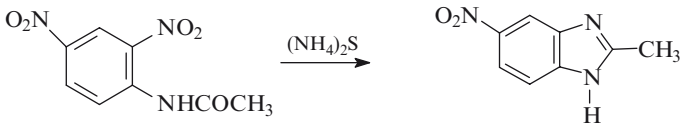
Scheme 2.40

Nitrobenzimidazoles

Benzimidazoles containing nitro group in the arylene fragment are obtained in the reaction of carboxylic acids or their derivatives with nitro-substituted 1,2-diaminobenzenes. This method is especially often used for the synthesis of 4-nitro- and 7-nitrobenzimidazoles, since the latter cannot be obtained by direct nitration of benzimidazoles. In most cases the reaction is carried out in the presence of HCl (the Phillips reaction) [46, 47, 52, 53, 75, 79, 100, 329–340]. Nitrobenzimidazoles

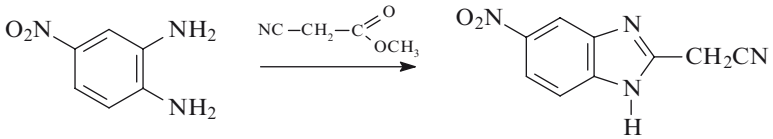
can also be obtained by simple boiling of 1,2-phenylendiamine nitro derivatives with excess lower aliphatic acids (formic or trifluoroacetic acid, for example) [61, 341–344]. Sometimes nitrobenzimidazoles can be obtained by heating the nitrated *ortho*-phenylendiamines, but in this case more rigorous conditions should be applied (the yields are significantly lower) [50, 345–347]. The cyclization is even a more difficult process when aromatic or heterocyclic acids are used [345]. In these conditions polyphosphoric acid is used as a condensing agent [329–340, 348]. Derivatives of acids may be employed in the synthesis of nitrobenzimidazoles in place of the acids themselves. More often anhydrides or chloroanhydrides are used for this purpose [44, 45, 50, 59, 256, 341–344, 349–352]. Usually this reaction is carried out in two stages: acylation of the correspondent 1,2-diaminonitrobenzenes with anhydrides or chloroanhydrides of carboxylic acids followed by cyclization of the forming *ortho*-aminoacylanilines [45, 50, 256, 349–353]. 1,2-Diaminobenzene nitro derivatives react with iminoesters [59, 354–362], nitriles [360, 363], hydrazides [364], and *ortho*-esters [365, 366] to form nitrobenzimidazoles.

A reaction of 4-nitro-1,2-phenylendiamine with benzotrichloride in the presence of sodium methylate [367] has been described. In this case 2-phenyl-5(6)-nitrobenzimidazole is obtained without preliminary extraction of the *ortho*-ester of benzoic acid. Sometimes acylated polynitroanilines, with one of the groups in the *ortho*-position to the amino group, are used as the initial products. On partial reduction of such compounds the cyclization to benzimidazoles takes place [85, 368]. For example, the reduction of 2,4-dinitroacetanilyde with ammonium sulfide has afforded 2-methyl-5(6)-nitrobenzimidazole (Scheme 2.41) [85].



Scheme 2.41

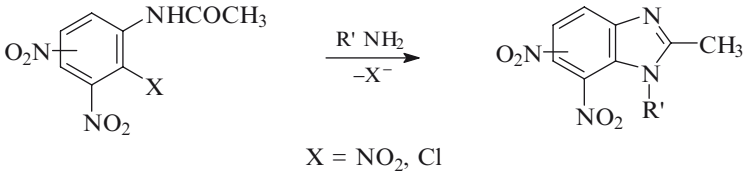
5(6)-Nitro-2-cyanomethylbenzimidazole, an intermediate in the synthesis of cyanine dyes, was prepared from 1,2-diamine-4-nitrobenzene and methyl cyanoacetate in nitrobenzene (Scheme 2.42) [369].



Scheme 2.42

The introduction of the nitro group in azoles leads to a long-wave shift of the visible absorption maximum and an enhancement of the sensitizing properties of cyanine dyes. A long-wave shift of the sensitivity of photographic materials is observed as well [369].

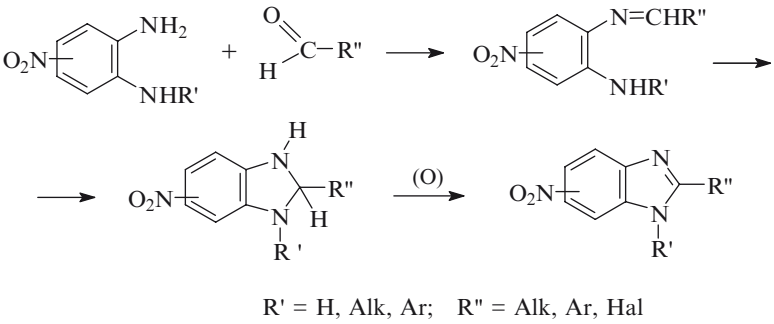
7-Nitrobenzimidazoles can be obtained in the reaction of primary amines with 2-R-3-nitroacetanylides (Scheme 2.43). On nucleophilic substitution the forming 2-NHR-3-nitroacetanylides transform to benzimidazoles without isolation [370].



Scheme 2.43

An interesting reaction has been described by Simonov and his colleagues [371]. Studying the reaction of some aromatic *ortho*-dinitro- and trinitrocompounds with benzylamine they have discovered that under special conditions the reaction of substitution of the nitro group with the benzylamine group is accompanied by reduction of the second nitro group and cyclization into 2-phenylbenzimidazole derivatives. In this case benzyl alcohol forming from benzylamine serves as a reducer. By the way it was obtained 4,5-dimethoxy-7-nitro-2-phenylbenzimidazole in 89% yield from 3,4,5-trinitroveratrole [371].

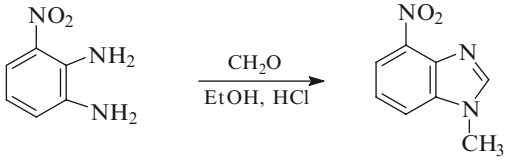
The reaction of 1,2-diaminonitrobenzenes with aldehydes is a widely accepted synthetic route to nitrobenzimidazoles [57, 62, 63, 66, 350, 372–383]. This reaction passes sequentially through a stage of the formation of azomethines (Schiff's base) and benzimidazolines. On oxidation the latter forms the corresponding benzimidazole derivatives (Scheme 2.44).



Scheme 2.44

Copper (II) salts are often used here as an oxidizer [62, 63, 66, 350, 374–379, 381–383], and atmospheric oxygen can also be used for this purpose [383]. For the preparation of nitrobenzimidazole derivatives the corresponding Shiff's bases are often boiled [57, 62, 63, 66, 372, 373, 380].

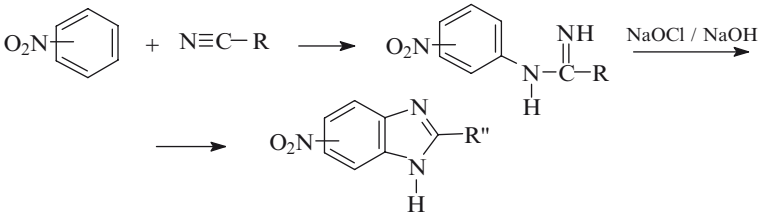
An easy and convenient method has been employed for the synthesis of 1-methyl-4-nitrobenzimidazole (Scheme 2.45) [384].



Scheme 2.45

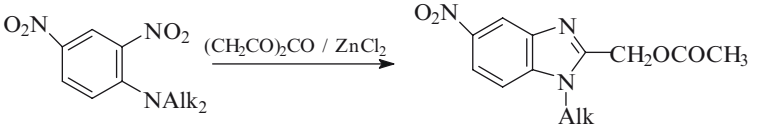
A one-stage reaction of 3-nitro-1,2-phenylendiamine with formaldehyde in an ethanol solution of hydrochloric acid leads to the formation of nitrobenzimidazole in high yield (77%) [384].

Nitroanilines react with organic cyanides in the presence of dry aluminum chloride. Under the influence of sodium hypochlorite in the presence of a base, the resultant amidines undergo cyclization to the corresponding benzimidazoles (Scheme 2.46) [385–388].



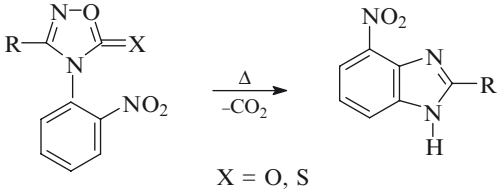
Scheme 2.46

2,4-Dinitroalkylanilines react with acetic anhydride in the presence of zinc chloride to form 2-acetoxymethyl-1-alkyl-5-nitrobenzimidazoles (Scheme 2.47) [389].



Scheme 2.47

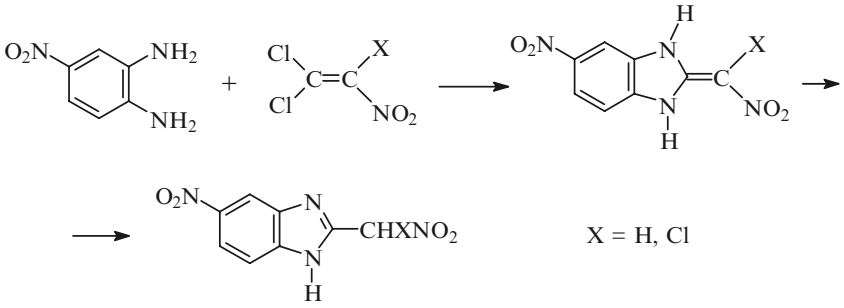
On thermal decomposition 3-substituted-4-nitrophenyl-1,2,4-oxadiazolones-5 form 2-substituted-4-nitrobenzimidazoles (Scheme 2.48) [390–393].



Scheme 2.48

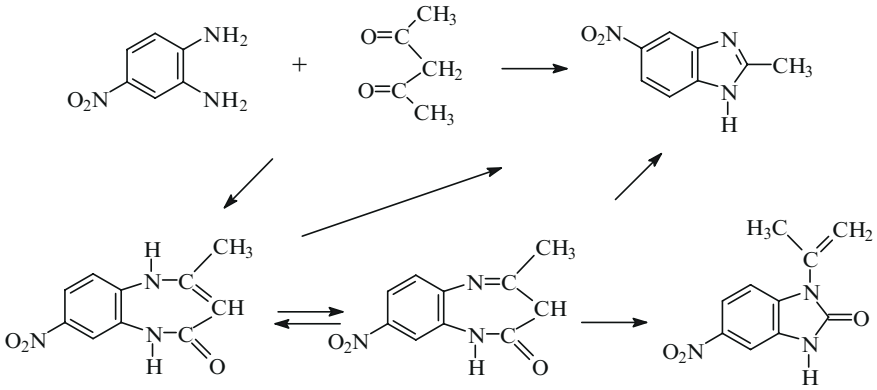
The reaction of *N*-butyl-2,4,6-trinitroaniline with NaOH in 60% 1,4-dioxane/H_2O affords 5,7-dinitro-2-propylbenzimidazole 3-oxide [394].

1,1-Dichloro-2-nitroethylene and trichloronitroethylene react with 4-nitro-1,2-phenyldiamine to afford nitrobenzimidazoles with the nitro group in both the phenylene fragment and side chain [395]. Evidently, the reaction mechanism consists in nucleophilic substitution of halogen atoms at the multiple bonds with subsequent prototropic rearrangement to the benzimidazole system, as shown in Scheme 2.49.



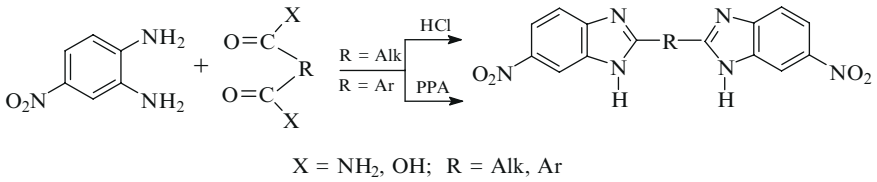
Scheme 2.49

2-Methyl-5-nitrobenzimidazole is formed on heating 4-nitro-1,2-phenylendiamine and its derivatives with the ester of acetoacetic acid (Scheme 2.50) [396, 397]. Depending on the experimental conditions, isomeric 8-nitro-4-methyl-2,5-dihydro-1*H*-1,5-benzodiazepinone-2 and 8-nitro-4-methyl-2,3-dihydro-1*H*-1,5-benzodiazepinone-2 easily transform into each other, and 5-nitro-1-isopropenylbenzimidazolone can be obtained (in this case).



Scheme 2.50

In a similar manner the bis(5-nitrobenzimidazolyl-2) derivatives were obtained (Scheme 2.51) [398].

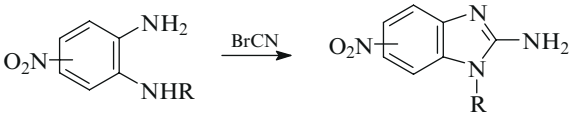


X = NH_2, OH; R = Alk, Ar

Scheme 2.51

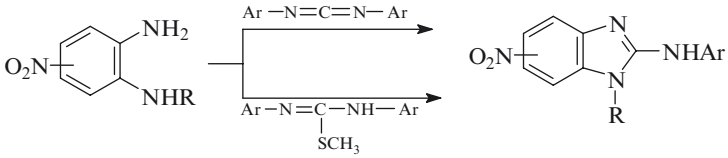
In the synthesis of aromatic derivatives polyphosphoric acid is used [398]. The synthesis of 1-(5-nitrobenzimidazolyl)-3-benzimidazolyl-2-oxapropane by the reaction of 4-(2-benzimidazolyl)-2-oxabutanoic acid hydrochloride and 4-nitro-*ortho*-phenylendiamine has been reported [399].

Like unsubstituted *ortho*-phenylendiamine, its nitro derivatives react with bromocyane to form the corresponding 2-aminobenzimidazoles (Scheme 2.52) [400–403].



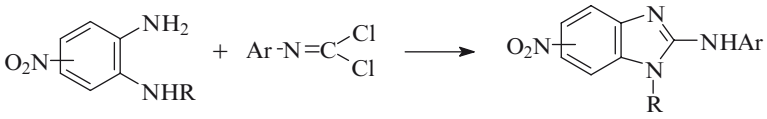
Scheme 2.52

Diarylcarbodiimines or derivatives of *S*-methylurea react with nitrated 1,2-diaminobenzenes in a similar way to lead to 2-arylaminobenzimidazoles (Scheme 2.53) [404, 405].



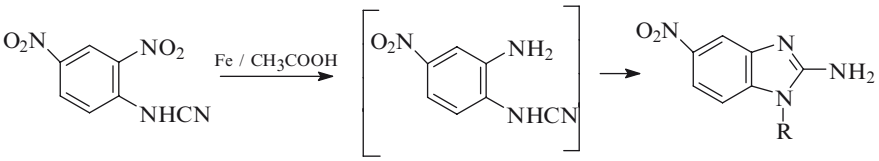
Scheme 2.53

The same products can be obtained with carboimidoyldichlorides as a reagent (Scheme 2.54) [406].



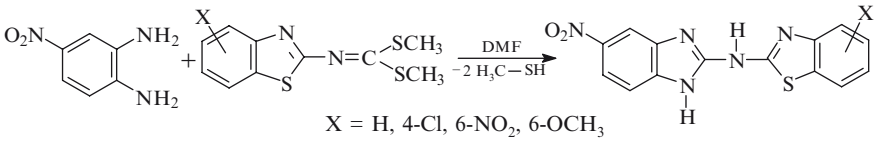
Scheme 2.54

A convenient synthesis of 2-amino-5(6)-nitrobenzimidazole involves reductive cyclization of 2,4-dinitrophenylcyanamide (Scheme 2.55) [407, 408].



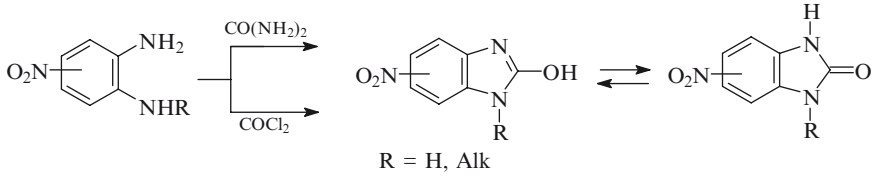
Scheme 2.55

2-(5-Nitrobenzimidazolyl-2-amino)-benzothiazoles are obtained from *ortho*-phenylenediamines and *S,S*-dimethyl-*N*-(2-bensothyazolyl)-carbonimido-dithioates in dimethylformamide (Scheme 2.56) [409].



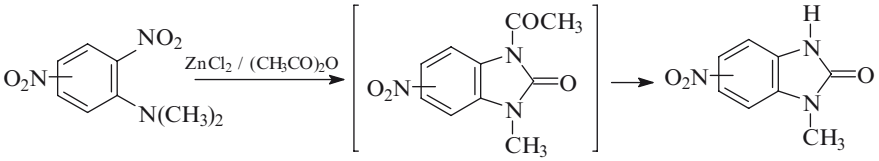
Scheme 2.56

The most widely spread synthetic route to benzimidazolone-2 nitroderivatives is provided by the reaction of *ortho*-phenylenediamine with phosgene or urea (Scheme 2.57) [105, 405, 407, 408, 410–412].



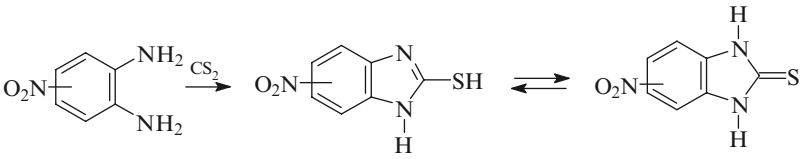
Scheme 2.57

1-Methyl-5- or 6-nitroderivatives were obtained as a result of intermolecular cyclization of *N,N*-dimethyl-2-nitro-5- or 5-nitroaniline with zinc chloride in acetic anhydride (Scheme 2.58) [411].



Scheme 2.58

Benzimidazolthione-2 nitroderivatives are obtained in a similar way under the influence of CS_2 (Scheme 2.59) [100, 407, 408, 413].

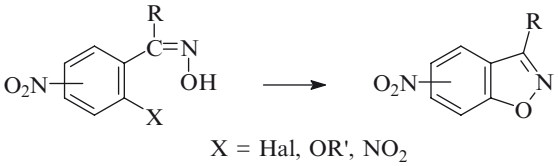


Scheme 2.59

A simple method for the preparation of 5-nitrobenzimidazolone-2, based on chemical [407, 408] or electrochemical reduction of 2,4-dinitrophenylurea [414], has been proposed. The electrochemical reaction occurs in a cell with an interelectrode space in aqueous solution of mineral acid at 85–95°C in the range of potentials from 0 to −200 mV relative to the silver electrode.

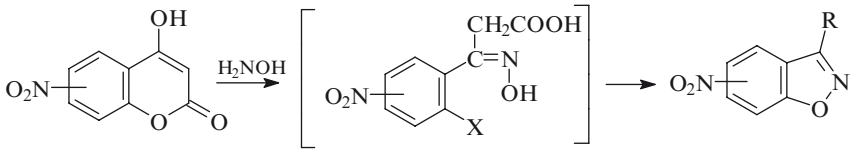
Nitrobenzisoxazoles, Nitrobenzoxazoles, and Nitrobenzoxadiazoles

The main method of producing 1,2-benzisoxazoles with the nitro group in the arylene fragment of the molecule is intermolecular condensation in an alkaline medium of the corresponding oxymes containing an easily eliminated group in the *ortho*-position (Scheme 2.60) [119, 298, 415–424].



Scheme 2.60

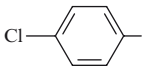
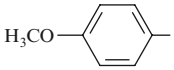
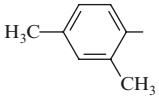
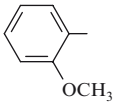
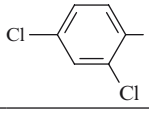
The same is true for halogens (bromine in most cases), hydroxy-, aryloxy-, or nitro group. The reaction of 4-hydroxycumarines with hydroxylamine proceeds in the same way (Scheme 2.61) [167, 419].



Scheme 2.61

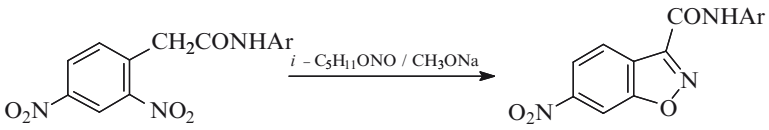
An attempt to substitute hydroxynitrocumarines by nitrocumarines failed: the yield of the final products fell to 5–17% [425].

Table 2 Characteristics of 3-substituted 6-nitro-1,2-benzisoxazoles

Ar	Yield (%)	mp (°C) (recryst.)	Ar	Yield (%)	mp (°C) (recryst.)
	60	214–216 (benzene)		50	236 (alcohol/ acetic acid)
	58	205–206 (CCl_4)		50	220–222 (alcohol/ acetic acid)
	40	211–214 (CCl_4)		65	228–230 (alcohol/ acetic acid)
	50	202 (CCl_4)		57	232 (alcohol/acetic acid)

In 1912, Borsche found out that the esters and amides of 6-nitro-1,2-benzisoxazole-3-carboxylic acid could be obtained in high yield in the reaction of isoamylnitrite with 2,4-dinitrophenylacetic acid derivatives in the presence of sodium methoxide [426].

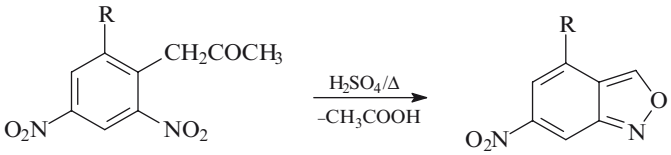
This reaction was successfully used for the preparation of arylamides of 6-nitro-1,2-benzisoxazole-3-carboxylic acid (Scheme 2.62 and Table 2.2) [427, 428].



Scheme 2.62

6-Nitro-1,2-benzisoxazolylketones can be obtained in an analogous manner [426]. 5-Nitrosalicilic aldehyde in an acid medium reacts with HN_3 to form a mixture of 5-nitro-1,2-benzisoxazole and 5-nitrobenzoxazole [429] – the latter being formed from 5-nitrosalicylic acid nitryl, a product of 5-nitro-1,2-benzisoxazole hydrolysis.

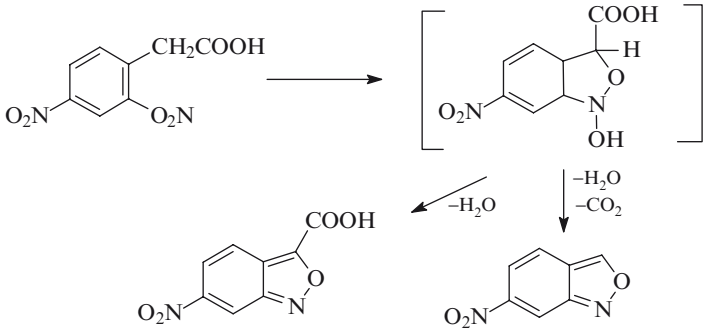
On heating with concentrated sulfuric acid 2,4-dinitrophenylacetone turns into 6-nitro-2,1-benzisoxazoles (Scheme 2.63) [430].



R = Cl (50 %), Br (49 %), I (46 %)

Scheme 2.63

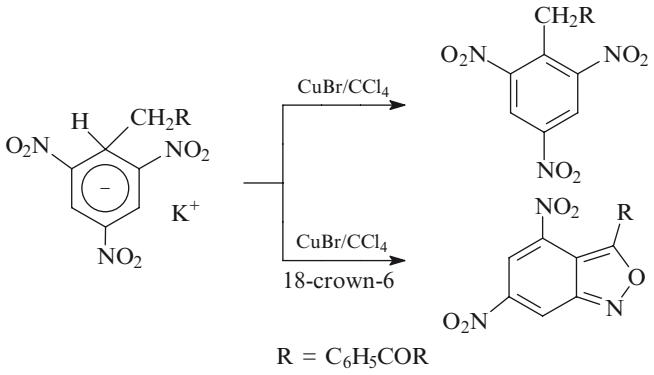
2,4-Dinitrophenylacetic acid reacts in a similar way and involves partial decarboxylation to form a mixture of 6-nitroanthranil-3-carboxylic acid and 6-nitroanthranil [431–433]. The reaction mechanism is a nucleophilic attack of the methylene carbon by the nitro group oxygen atom, as shown in Scheme 2.64. The formed cyclic product undergoes dehydration or dehydration with simultaneous decarboxylation.



Scheme 2.64

The methylene ester of 6-nitro-2,1-benzoxazole-3-carboxylic acid is obtained in a similar manner [434]. The reaction of oxidation of 1,3,5-trinitrobenzene σ-complexes, containing the C–C bond in the side chain, follows an interesting pathway [434].

Under the influence of oxidizing systems [copper(I) bromide – CCl_4] these systems are oxidized into the corresponding 1,3,5-trinitrobenzene derivatives, whereas in the presence of the same system and crown esters (e.g., 18-crown-6) 4,6-dinitroanthranils are formed (Scheme 2.65). So, the presence of the group in the geminal center of the σ-complex is a necessary condition for conversion of this type [435].

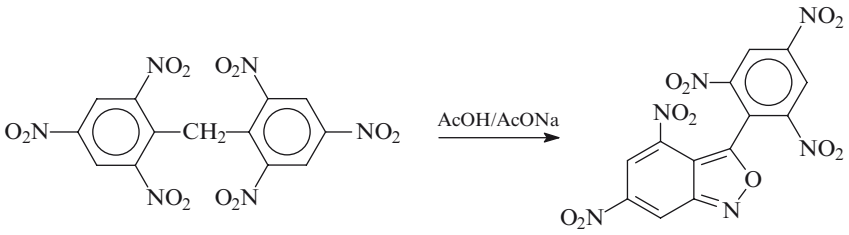


Scheme 2.65

3-Aryl-6-nitroanthranils are obtained on heating of 2,4-dinitrobenzaldehydes in sulfuric acid or polyphosphoric acids with aromatic carbohydrates [436–440]. Reductive heterocyclization of 2,6-dinitrobenzaldehyde in the presence of 2-bromo-2-nitropropane

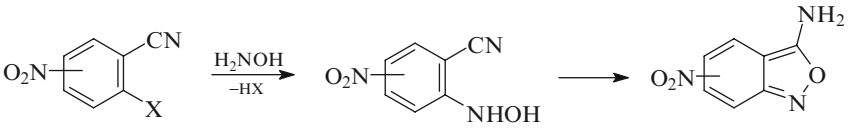
and indium (2:5) in an MeOH/H_2O solution leads to 4-nitro-2,1-benzisoxazole in good yield [425]. 3,6-Dichloro-2,5-dinitro-*p*-xylol on heating in oleum transforms to 4,7-dichloro-5-nitro-6-methyl-2,1-benzisoxazole [442, 443].

In the reaction with sodium acetate 2,2′,4,4′,6,6′-hexanitrodiphenylmethane undergoes an intermolecular cyclization, giving in a good yield 3-picryl-4,6-dinitroanthranil, a rather thermally stable explosive (Scheme 2.66) [444].



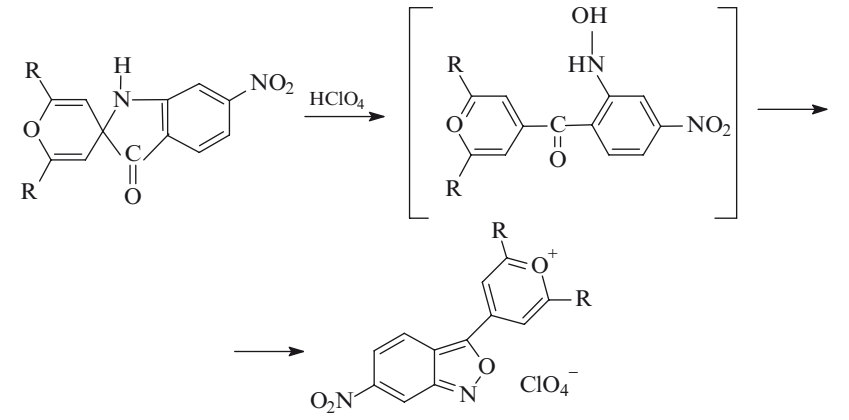
Scheme 2.66

2,1-Benzisoxazoles are obtained from *ortho*-nitroacetylbenzenes in the reaction with 3-phenylphosphate. 2-Amino-4-nitropropiophenone was obtained in the presence of a nitro group in the benzene ring along with nitroanthranil [445]. In hydrochloric acid the cyclization is accompanied by chlorination of the phenylene fragment [446]. The nitriles of *ortho*-halogenonitrobenzoic acids react with hydroxylamine to form nitrated 3-amino-2,1-benzisoxazoles (Scheme 2.67) [447].



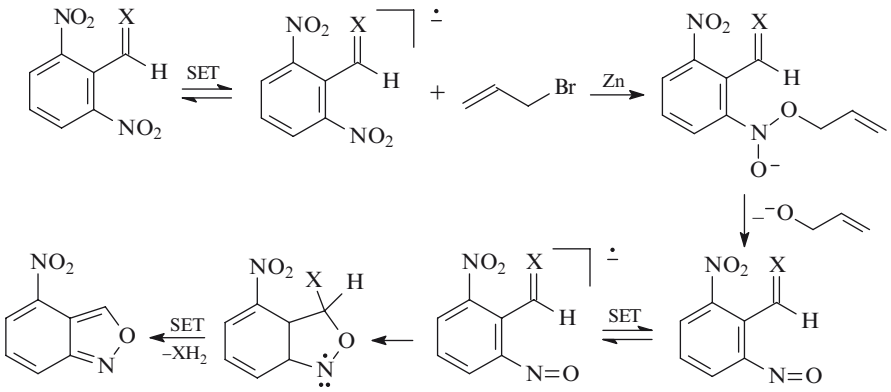
Scheme 2.67

(6-Nitro-2,1-benzisoxazolyl-3)pyrilium perchlorates have been obtained from the corresponding oxaspiroindolines (Scheme 2.68) [448].



Scheme 2.68

A mild and novel reaction route to 2,1-benzisoxazoles from 2-nitrobenzaldehydes in the presence of allyl bromide and zinc dust has been established [449]. The reductive cyclization of 2,6-dinitrobenzaldehyde was strongly retarded probably because of the inhibitory effect of the second nitro group [441, 449]. The authors assume a radical mechanism of the reaction, as demonstrated in Scheme 2.69 [449].



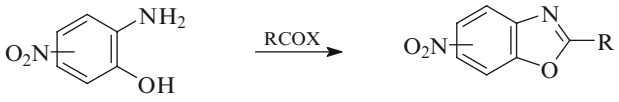
SET – single electron transfer, X = O, N-Ph

Scheme 2.69

This way would provide a useful synthetic technique along with reductive *N*,*O*-diallylation of nitrobenzene.

6-*tert*-Butyl-5-methoxy-4-nitro-2,1-benzisoxazole along with other products have been isolated on photolysis of 4-*tert*-butyl-3-methoxy-2,6-dinitrotoluene [450].

Nitrobenzoxazoles possessing nonlinear optical properties [451], like their nonnitrated analogs, are easily obtained in the reaction of the corresponding *ortho*-aminophenols with carboxylic acids [452–458], aldehydes [459, 460], or chloroanhydrides [134, 461–464] (Scheme 2.70).



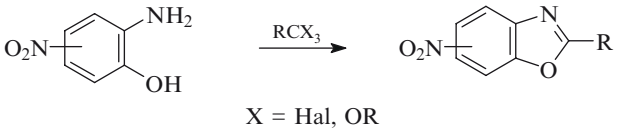
X = H, OH, Cl

Scheme 2.70

Mono- or diacyl derivatives that undergo cyclization to benzoxazoles on heating or under the influence of dehydrating agents are formed as intermediates in this reaction [134, 452, 453, 459, 461–473]. Phosphorus oxychloride [453, 457], boric anhydride [455, 461, 462], or polyphosphoric acid [134, 471] are used as condensing agents. In particular, 2-hydroxy-5-nitrobenzoxazole, used for the synthesis of antivirus medicines, has been obtained by the reaction of condensation of 4-nitro-2-aminophenol with $(NH_2)_2CO$ in pyridine [474].

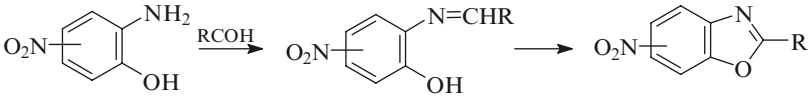
To prepare 2-trichloromethylbenzoxazole, nitrated *ortho*-aminophenoles are treated with iminoesters of trichloroacetic acid [52, 475, 476]. Some other 2-substituted nitrobenzoxazole derivatives were obtained in the same way [134, 360, 361].

For the formation of the benzoxazole cycle, compounds containing trichloromethyl [477, 478] or trialkoxymethyl groups can be made use of (Scheme 2.71) [478–480].



Scheme 2.71

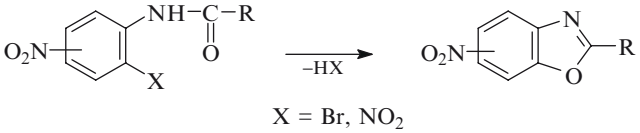
Nitrated *ortho*-aminophenols react with aldehydes to form Schiff's bases, which are easily oxidized into the corresponding benzoxazoles (Scheme 2.72) [481].



Scheme 2.72

Lead acetate [134, 482–484], nickel peroxide [445, 485, 486], and some other substances [487–489] are used as oxidants in most cases.

Sometimes, the corresponding *ortho*-bromo- or *ortho*-nitroacylanilides are used in place of aminophenols for the synthesis of nitrobenzoxazoles (Scheme 2.73) [490, 491].



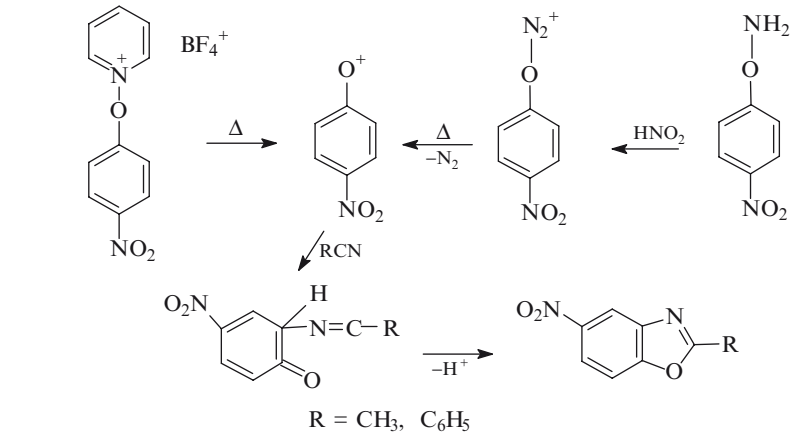
Scheme 2.73

N-aryloxypyridinium salts or diazotized aryloxyamines on heating generate aryloxene ions, which turn into benzoxazoles in the presence of acetonitrile or benzonitrile, as shown in Scheme 2.74 [492, 493].

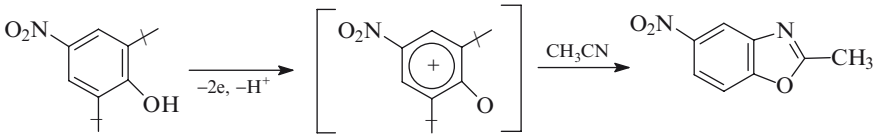
Suschitzky et al. have proposed an original synthesis of benzoxazole nitro derivatives in a mixture of carboxylic and polyphosphoric acids by heating aromatic aldehydes containing the nitro group in the *para*-position [471].

7-*tert*-Butyl-2-methyl-5-nitrobenzoxazole has been synthesized by electrochemical oxidation of 4-nitro-2,6-di-*tert*-butylphenol in acetonitrile (Scheme 2.75) [494].

7-*tert*-Butyl-4-methyl-5-nitrobenzoxazole and 6-*tert*-butyl-5-methoxy-4-nitro-2,1-benzisoxazole were found among the products of photolysis of 4-*tert*-butyl-3-methoxy-2,6-dinitrotoluene [450].

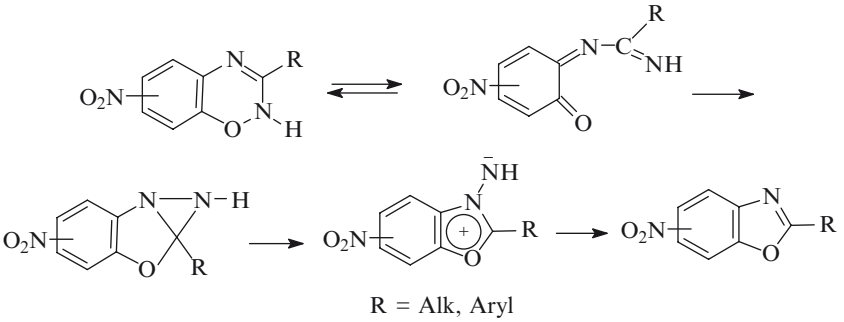


Scheme 2.74



Scheme 2.75

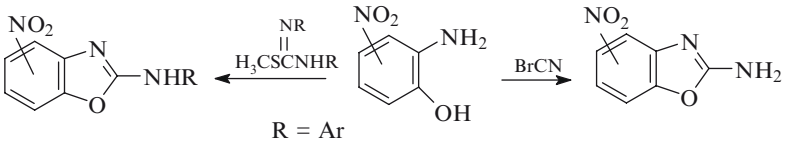
When heated, benzoxadiazines give benzoxazoles in good yield [495, 496]. The intermediate formation of *ortho*-quinonimine has been suggested on the basis of the proposed recyclization mechanism (Scheme 2.76).



Scheme 2.76

Heating of 7-nitro-1,2,4-benzoxadiazine-3-carboxylic acid or basic hydrolysis of its ethyl ester results in 2-amino-6-nitrobenzoxazole [495, 496]. Earlier this compound was wrongly ascribed the structure of 7-nitro-1,2,4-benzoxadiazine [497].

Nitrated 2-aminobenzoxazoles are obtained in good yield in the reaction of *ortho*-aminophenols with cyanogen bromide [498–500] or with *S*-methylisothiourea derivatives (Scheme 2.77) [501].

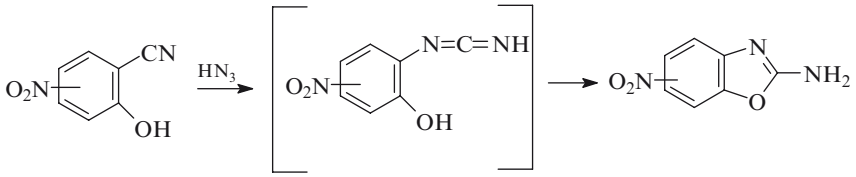


Scheme 2.77

5- or 6-Nitrobenzoxazoline-2-thiones react with morpholine and aromatic amines to form 2-aminobenzoxazoles [502]. When butylamines and some other amines are used the reaction stops at a stage of the formation of thiourea 2-oxyphenyl derivatives and for further cyclization to 2-aminobenzoxadiazoles the presence of silver salts is necessary (Scheme 2.78).

Scheme 2.78

The nitrile of salicylic acid and its nitroderivatives reacts with HN_3 to form 2-aminobenzoxazoles, as illustrated in Scheme 2.79 [503, 504].



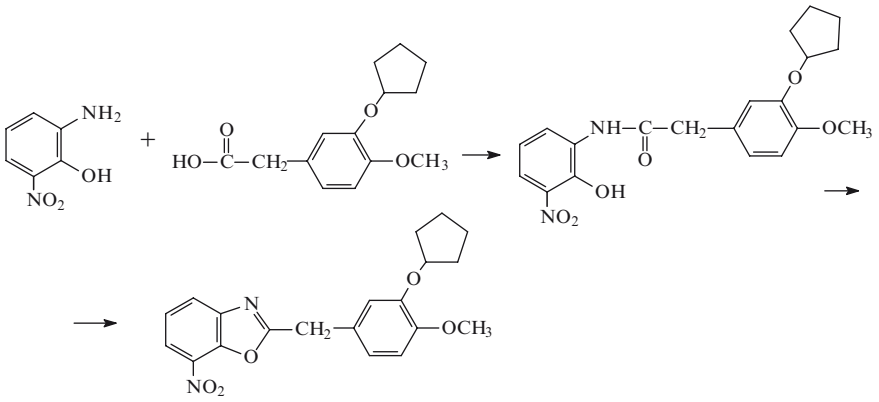
Scheme 2.79

2-(3-Cyclopentyloxy-4-methoxybenzyl)-7-nitrobenzoxazole used in the therapy of asthma has been obtained by condensation of *N*-(2-hydroxy-3-nitrophenyl)-3-cyclopentyloxy-4-methoxyphenylacetamide (Scheme 2.80) [505].

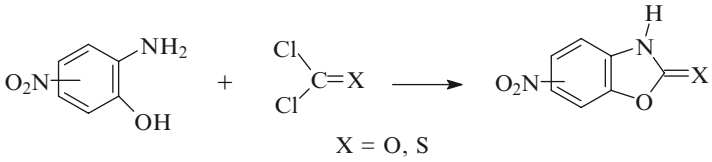
2-Thiol-5-nitrobenzoxazole, the structural material for the preparation of potential enantioselective inhibitors of leukotriene biosynthesis, has been synthesized by condensation of nitro-*ortho*-aminophenole with CS_2 [506].

Nitroderivatives of *ortho*-aminophenols react with phosgene and thiophosgene to form benzoxazolones-2 [507] and benzoxazolthiones-2, [508] respectively (Scheme 2.81).

Synthesis of nitrobenzoxazolones-2 by Beckman's rearrangement of 4-nitrosalicylhydroxamine acid has been reported [509]. The process is carried out on heating (4-nitro-2-oxyphenyl)-urea [510] or 4-(4-nitro-2-oxyphenyl)semicarbazide [511] with mineral acids and by oxidation of 6-nitro-2-hydroxymethylquinoline and its derivatives.



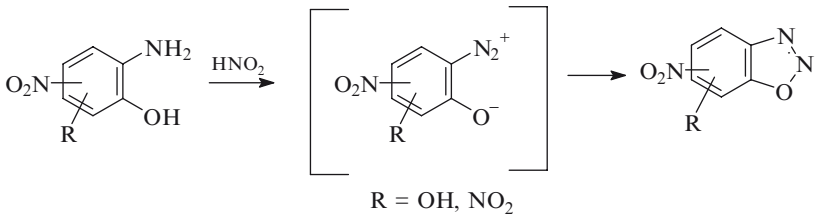
Scheme 2.80



Scheme 2.81

The most widespread preparative synthetic route to nitrobenzoxazolothione-2 is the reaction of nitroaminophenols with CS_2 [501, 512, 513].

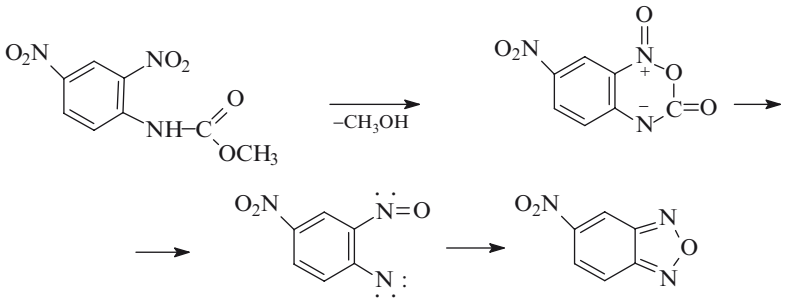
Nitroderivatives of *ortho*-aminophenole on diazotization form the corresponding *ortho*-diazophenols, which readily undergo cyclization into 1,2,3-benzoxadiazoles (Scheme 2.82) [513–518].



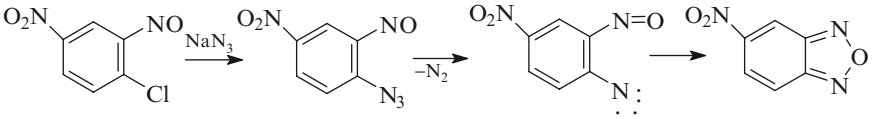
Scheme 2.82

On pyrolysis of methyl-*N*-(2,4-dinitrophenyl)carbamate 5-nitro-2,1,3-benzoxadiazole (5-nitrobenzofurazan) was isolated in a yield of 35% (Scheme 2.83) [519].

The key product in this process is *ortho*-nitrozophenylnitrene from which benzofurazan is formed later. The reaction of 2-chloro-5-nitronitrozobenzene with sodium azide in an aqueous acetone medium is likely to follow a similar pathway. In this case the yield of 5-nitrobenzofurazan reaches 73% (Scheme 2.84) [520].

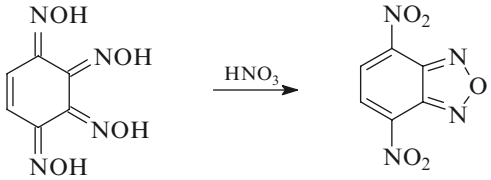


Scheme 2.83



Scheme 2.84

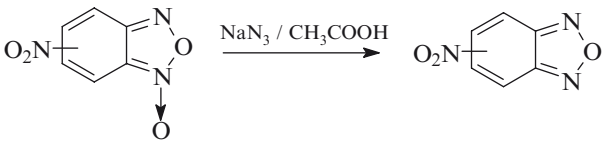
In the reaction of nitric acid with tetraoximecyclohex-5-ene-1,2,3,4-tetraone, the oxidation of two oxyme groups with simultaneous cyclization to 4,7-dinitro-2,1, 3-benzoxadiazole takes place (Scheme 2.85) [521].



Scheme 2.85

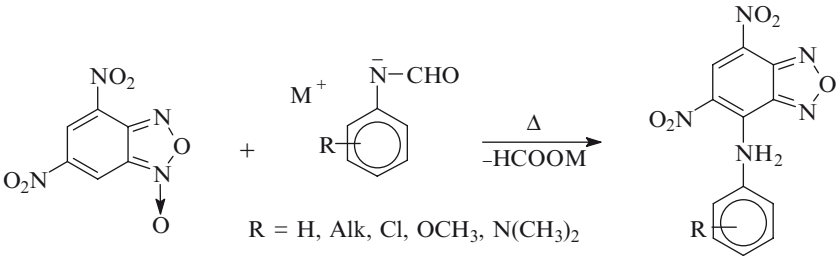
The most common method of the synthesis of nitrobenzofurazans is reduction of benzofuroxan nitroderivatives. A lot of examples of the synthesis of nitro-2,1, 3-benzoxadiazoles from the corresponding *N*-oxides have been described [149, 155, 156, 522–526]. Here, the results of electrochemical investigations of a more difficult reduction of exocyclic N→O bond, in comparison with the endocyclic one, look unexpected [527]. The following explanation for this apparent contradiction can be given. On the one hand, the process of chemical reduction can differ significantly from the mechanism of electrochemical reduction. On the other hand, the primary opening of the furoxan cycle with subsequent closing into furazan is possible; it is the endocyclic N→O bond that undergoes primary opening. Triphenylphosphine is used as a reducing agent in most cases [149, 155, 523, 524].

On heating of sodium azide with benzofuroxans in ethylenglycole or DMSO the corresponding benzofurazans are formed [523, 525]. If the reaction is carried out in a medium of acetic or *iso*-butyric acids, that is, actually using HN_3, the nitrobenzofurazans sought are formed in good yield (Scheme 2.86) [526].



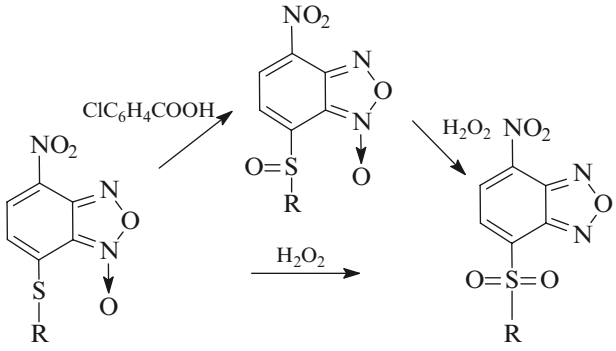
Scheme 2.86

4,6-Dinitrobenzofurazan 7-aminoderivatives have been obtained by the reaction of 4,6-dinitrobenzofuroxan with alkali metal salts of the corresponding formanylidines (Scheme 2.87) [527–529].



Scheme 2.87

On oxidation of 4-nitro-7-arylthiobenzofuroxanes with excess hydrogen peroxide the corresponding sulfonylbenzofurazans are obtained, whereas in mild conditions (*meta*-chloroperoxobenzoic acid, 0–20°C) intermediate nitro derivatives of sulfonylbenzofuroxan were isolated (Scheme 2.88) [530].



Scheme 2.88

On heating, the latter form 4-nitro-7-arylsulfonylbenzofurazans in high yield. In this case the observed migration of the furoxan cycle exocyclic oxygen to the neighboring

sulfoxide group follows an intermolecular mechanism. The rate of this rearrangement increases with introducing electron-donating substituents into the phenyl ring of the sulfoxide fragment. It should be noted that the oxygen atom migration from the furoxan ring moves only to the sulfoxide group and not to the sulfide one. In some cases the reaction goes without intermediate isolation of the furoxan cycle. For example, on heating 1,3-diamino-2,4,6-trinitrobenzene 4-amino-5,7-dinitrobenzofurazan is formed.

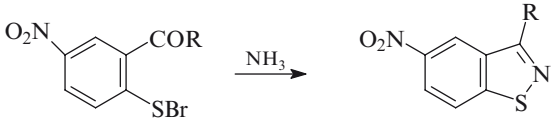
In recent years, particular attention focuses on reactivity of nitrobenzofuroxans and nitrobenzofurazans [531]. The latest are represented as a class of neutral 10-π-electron-deficient heteroaromatic substrates that exhibit an extremely high electrophilic character in many covalent nucleophilic addition and substitution processes.

Nitrobenzisothiazoles, Nitrobenzothiazoles, and Nitrobenzothiadiazoles

Nitroderivatives of aromatic aldehydes or ketones, containing sulfohalogen group in the *ortho*-position, undergo cyclization into the corresponding 1,2-benzisothiazoles under the influence of ammonia (Scheme 2.89) [173].

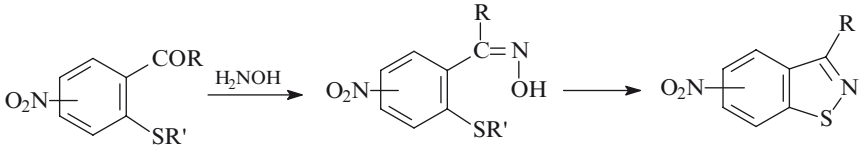
Later this process has been significantly simplified by using *ortho*-chloro substituted aldehydes or ketones as the initial products [532–536].

Another rather widely accepted synthesis of the aforementioned compounds is



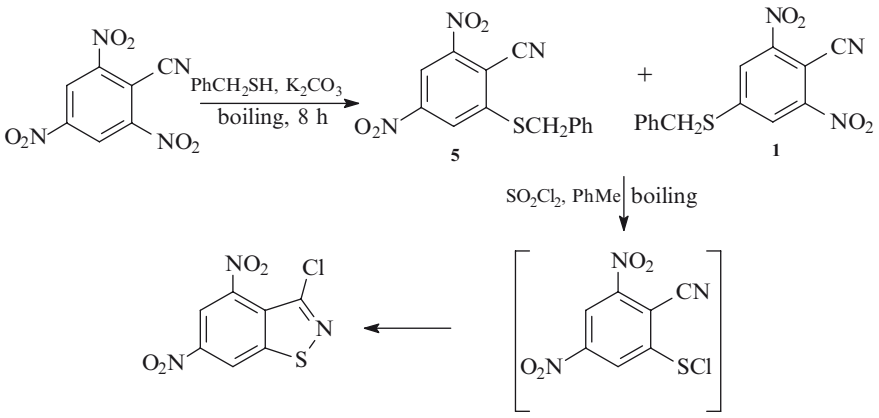
Scheme 2.89

the condensation of oximes of aldehyde or ketone nitro derivatives, containing sulfohydryl or sulfoalkyl groups in the *ortho*-position (Scheme 2.90) [166, 537, 538].



Scheme 2.90

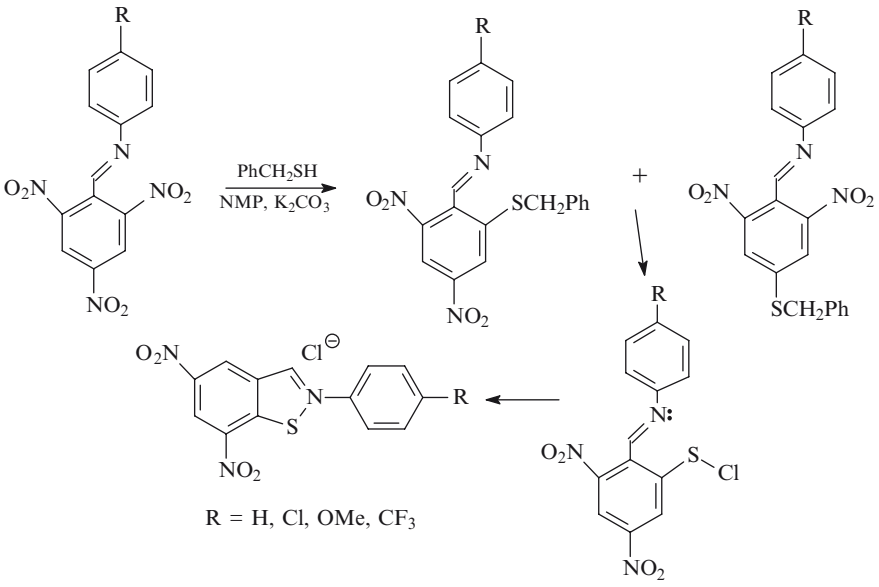
4,6-Dinitrobenzisothiazole derivatives and salts were prepared in the course of utilization of explosive 2,4,6-trinitrotoluene [539–541]. 3-Cloro-4,6-dinitrobenzisothiazole was prepared on using 2,4,6-trinitrotoluene, which can easily be transformed to 2,4,6-trinitrobenzonitrile (TNBN) by treatment with nitrosyl chloride [539]. The reaction of TNBN in the presence of K_2CO_3 led to both *ortho* and *meta* isomers, the products of substitution of NO_2 groups by a $PhCH_2S$ unit, with the ratio of isomers being dependent on the solvent polarity (Scheme 2.91).



Scheme 2.91

The fraction of *ortho* substitution considerably is increased with decreasing solvent polarity. The mixture (5:1) of *ortho* and *meta* isomers prepared in toluene was treated with SO_2Cl_2 to give 3-cloro-4,6-dinitrobenzisothiazole as a result of intramolecular cyclization [539].

2-Aryl-4,6-dinitrobenzisothiazolium chlorides can be obtained even at room temperature by treatment of the corresponding sulfuryl chlorides in dichloroethane without separation, as shown in Scheme 2.92 [540].

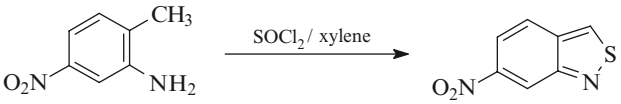


Scheme 2.92

Similarly to 1,2-benzisoxazoles, 1,2-benzisothiazoles with the nitro group in the arylene fragment can be obtained from 4-mercaptotocumarines and from hydroxylamine [167].

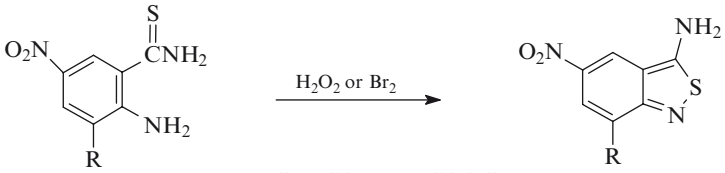
Synthesis of 5-nitro-1,2-benzisothiazolone-3 possessing thrombolytic and antibacterial activity has been described in reference [542].

The data on the synthesis of nitrated 2,1-benzisothiazoles are rather scarce in comparison with the corresponding benzisoxazoles. It has been reported that, like other 2-aminotoluenes, 2-amino-4-nitrotoluene reacts with thionyle chloride in xylene to form 6-nitro-2,1-benzisothiazole, whereas 2-amino-5-nitrotoluene does not enter into this reaction (Scheme 2.93) [543].



Scheme 2.93

3-Amino-5-nitro-2,1-benzisothiazole and its 7-substituted derivatives are obtained on oxidation of 5-nitro-2-amino-3-R-thiobenzamides with hydrogen peroxide or bromine (Scheme 2.94) [544–546].

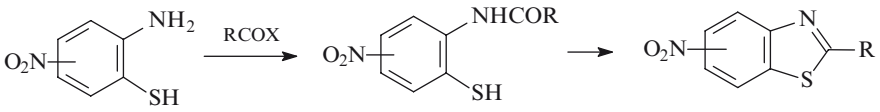


R = H, CN, $CONH_2$, $COOCH_3$

Scheme 2.94

In these conditions 5-nitrothioanthranilic acid is oxidized to 5-nitro-2,1-benzisoxazolone-3 [128, 547].

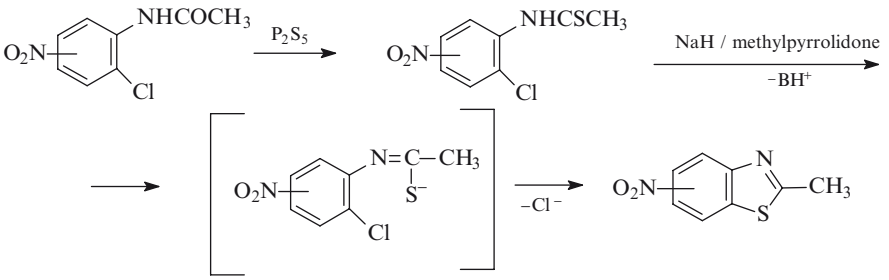
One of the most convenient and widespread syntheses of benzothiazole nitroderivatives is the reaction of the corresponding *ortho*-aminothiophenols with acids [134, 548–551], their anhydrides [195, 550, 552], chloroanhydrides [553] or benzaldehydes [554] according to Scheme 2.95.



X = OH, OCOR', Cl; R = H, Alk, Ar

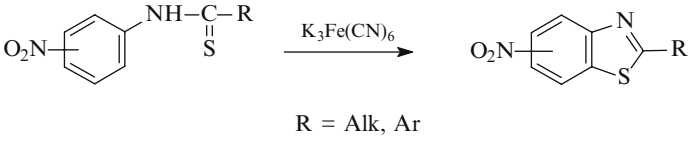
Scheme 2.95

ortho-Acetylaminothiophenols, which readily undergo cyclodehydratation, are intermediate products in these reactions [134, 555]. In this case *ortho*-acetylaminothiophenols are often not separated; instead, *ortho*-halogenoacylanilines are treated with alkali metal sulfides [183, 556–561]. In a modification of this process, *ortho*-halogenothioacylanilines are boiled with phosphorus pentasulfide in benzene, and the products, nitroaniline thioacylderivatives, undergo cyclization to nitrobenzothiazoles in amide solvents in the presence of bases (Scheme 2.96) [562, 563].



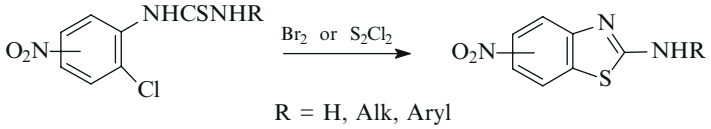
Scheme 2.96

Like other benzothiazoles, nitrobenzothiazoles can easily be obtained by Yakobson's method from thioacylanylides under the influence of potassium ferricyanide (Scheme 2.97) [564–567].



Scheme 2.97

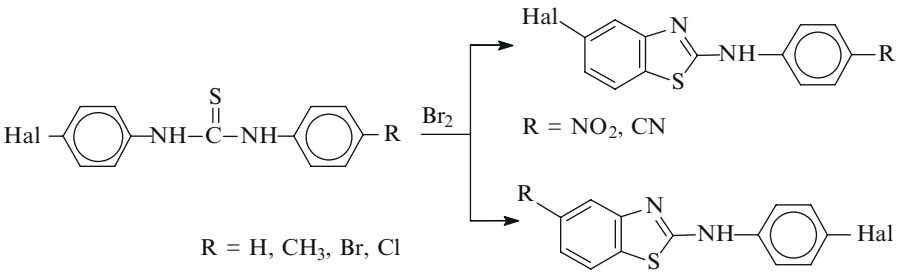
Later 2-methyl-6-nitrobenzothiazole was obtained by electrochemical oxidation of 4-nitrothioacetanylide [568]. Interestingly, there is no cyclization under the influence of potassium ferricyanide when arylthioureas are used. In this case other cyclizating agents have to be used as oxidizers. Bromine-induced oxidation of nitroarylthiourea with the formation of the corresponding 2-aminobenzothiazole nitroderivatives (Hugershoff's method) is used for preparative purposes [182, 569–574]. Sometimes sulfur monochloride is used as an oxidizer in place of bromine (Scheme 2.98) [575, 576].



Scheme 2.98

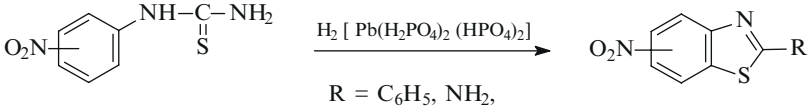
Introduction of the diazoarylamino groups into position 2 of 6-nitrobenzothiazoles leads to the thermal stability of nonlinear optical organic materials on the base nitrobenzazoles [577].

With *N*,*N*′-diarylthioureas the cyclization direction is determined by the character of substituents, and the introduction of a nitro group or other electron-withdrawing substituents decreases the reactivity of the aromatic ring [179]. This can be illustrated by the following Scheme 2.99.



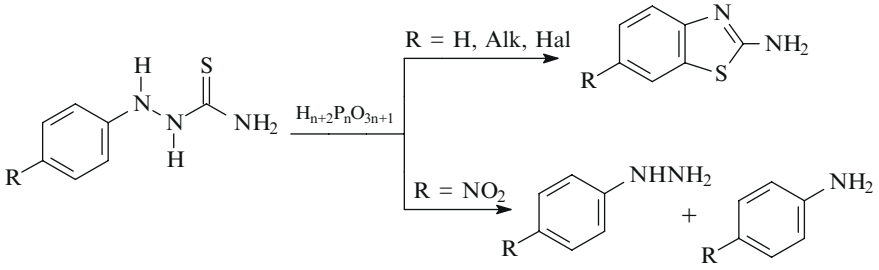
Scheme 2.99

The use of a mixture of Pb_3O_4 with *ortho*-phosphoric acid as an oxidizer allows the preparation of both 2-aryl- and 2-aminonitrobenzothiazoles (Scheme 2.100) [487].



Scheme 2.100

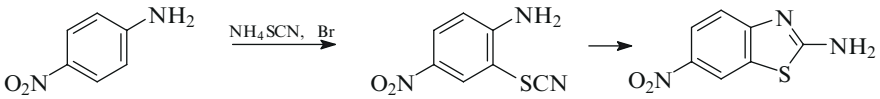
On heating in polyphosphoric acid 1-phenylthiosemicarbazides with alkyl or halogen substituent in the benzene ring turn into 2-aminobenzothiazoles in good yield (Scheme 2.101) [578].



Scheme 2.101

However, the presence of the nitro group in the *para*-position to the thiosemicarbazide group blocks the process of cyclization, and only the products of N–C and N–N bond splitting are obtained as a result.

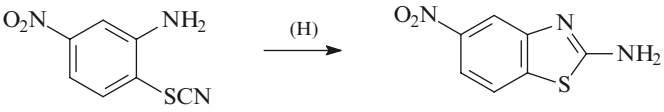
4-Nitroaniline reacts with ammonium rhodanide and bromine to form 2-rhodanyl-4-nitroaniline, which undergoes cyclization into 2-amino-6-nitrobenzothiazole under the reaction conditions on Scheme 2.102 [579–582].



Scheme 2.102

Other derivatives of 2-nitroaminobenzene were obtained in the same way [550, 580, 583], and in some cases the aforementioned rhodanylaniniles could be isolated [550, 583].

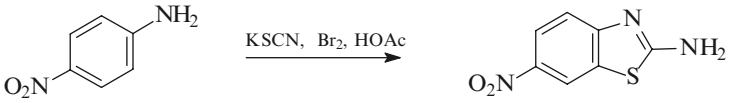
It should be taken into consideration that the rhodanation of substituted anilines goes mainly to the position 4. The reported synthesis of 2-amino-4-nitrobenzothiazole by rhodanation of *ortho*-nitroaniline [583] turned out to be incorrect. In fact, the authors obtained 2-nitro-4-rhodanylaniline of the same empirical formula [584, 585]. 2,4-Dinitrophenylthiocyanate is reduced to 2-amino-5-nitrobenzothiazole in acetic acid by iron (Scheme 2.103) [407, 408].



Scheme 2.103

The same compound can be obtained on heating 2,4-dinitrochlorobenzene with thiourea in sulfolane [586]. In the same manner 2-amino-7-trifluoromethyl-5-nitrobenzothiazole and 2-amino-7-nitrobenzothiazole were synthesized.

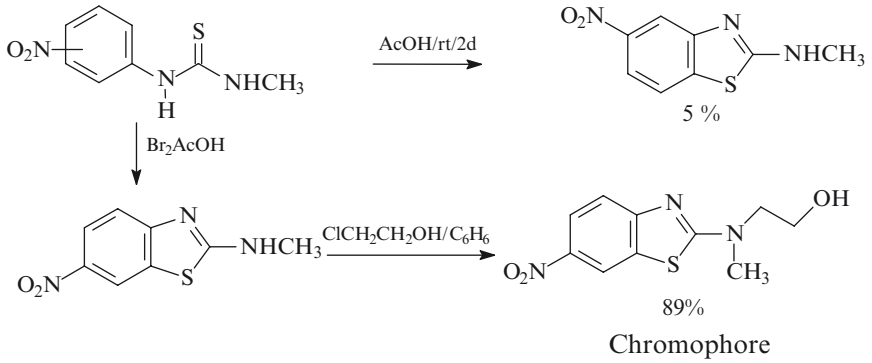
2-Amino-6-nitrobenzothiazole as a sodium flux inhibitor (anticonvulsant activity) has been synthesized from nitroaniline via a one-pot procedure (Scheme 2.104) [587].



Scheme 2.104

In this route, the thiourea is produced in situ and then oxidatively cyclized to the nitrobenzothiazole. This method failed for anilines containing an electron-withdrawing substituent in the *meta*-position.

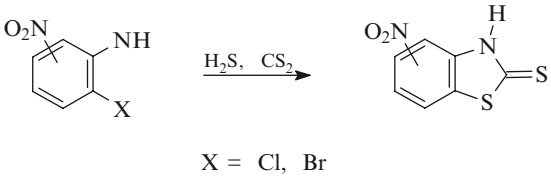
Nitrobenzothiazole chromophores [588, 589] and their precursors [590] are building blocks of nonlinear optical materials, which are extensively used in the field of optical information processing, optical sensing, data storage, and telecommunications [588, 591]. 5-Nitro- [590] and 6-nitro-2-(methyamino)benzothiazole [589] have been prepared from 3-nitro- and 4-nitrophenylthiourea correspondingly, as illustrated in Scheme 2.105.



Scheme 2.105

Preparation method of the chromophore involves the condensation of *para*-nitroaniline with thiocyanate in methanol and the bromine radical cyclization using bromine in acetic acid. In this case only one product – 2-(methylamino)-6-nitrobenzothiazole – was obtained, which is easily purified over column chromatography using neutral alumina [589].

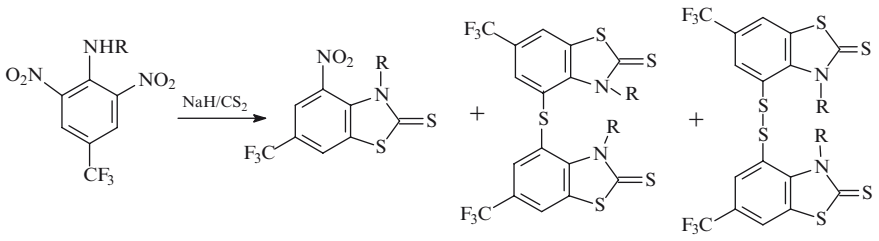
6-Methyl-5-nitrobenzothiazolone-2 has been obtained from (5-methyl-2,4-dinitrophenylthio)acetic acid and acetic anhydride [592]. Benzothiazolethione-2 nitroderivatives can readily be obtained by the following Scheme (Scheme 2.106) [184, 559].



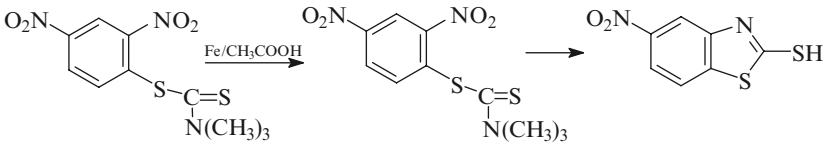
Scheme 2.106

An analogous reaction takes place with *ortho*-nitroanilines. For example, 4-amino-3,5-dinitrobenzotrifluoride and its *N*-alkylsubstituted derivatives react with CS_2 in dry dimethylformamide in the presence of sodium hydride to form the corresponding benzothiazolethiones (Scheme 2.107) [593].

2,4-Dinitrophenyl ester of *N*,*N*-dimethyldithiocarbamic acid is reduced with iron powder in glacial acetic acid with the formation of 5-nitrobenzothiazolethione-2 [407, 408] (Scheme 2.108), which is extensively used in coordinating chemistry [594–597].



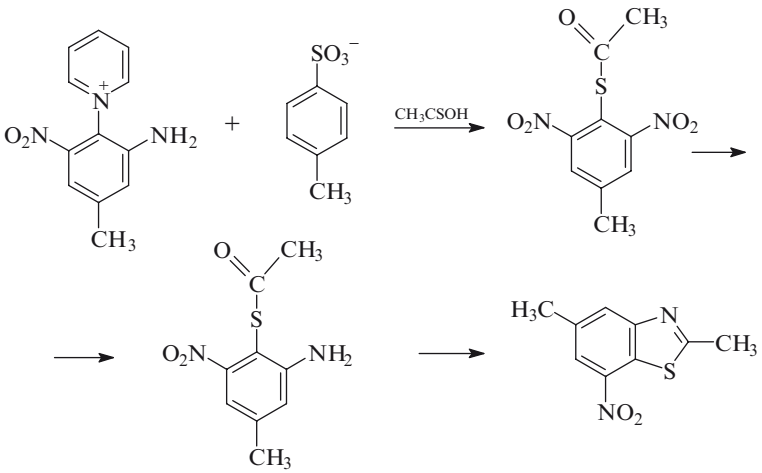
Scheme 2.107



Scheme 2.108

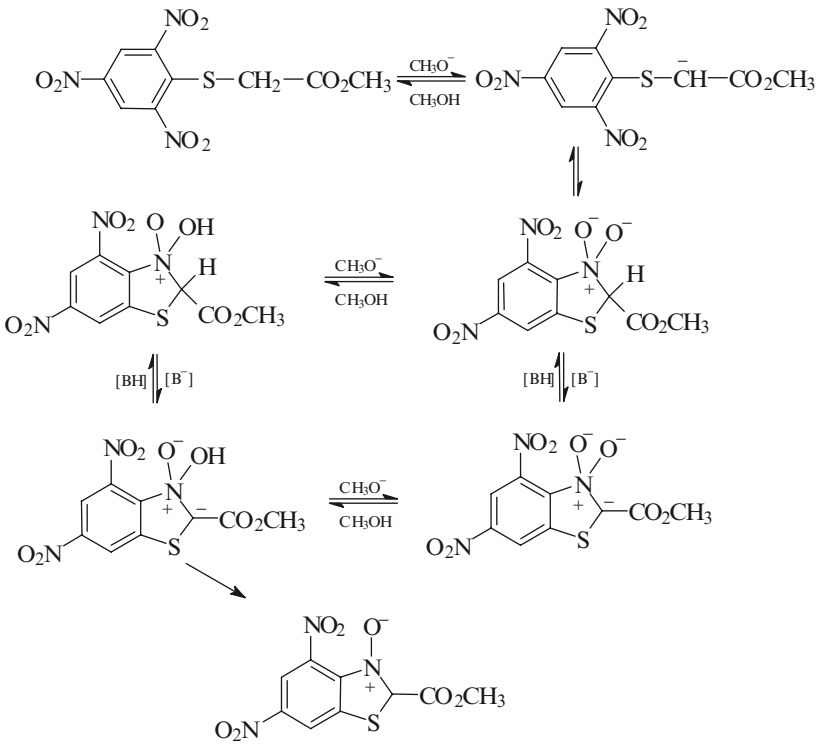
The heteroaromatic thioles, in particular 2-mercapto-6-nitrobenzothiazole, were studied in regard to their abilities to function as coinitiators in free-radical photopolymerizations induced by camphorquinone and isopropylthioxanthone [598].

Formation of 2-propyl-5-nitrobenzothiazole on reduction of 2,4-dinitro-butylthiobenzene with sodium polysulfite or trimethylphosphite has been observed [599]. *para*-Toluenesulfonate 2,5-dimethyl-7-nitrobenzothiazole was obtained under the action of excess thioacetic acid on *N*-(4-methyl-2,6-dinitrophenyl)pyridinium [600]. The reaction involves the formation of 4-methyl-2,6-dinitrothiophenol acetate in which, under experimental conditions, one of the nitro groups is reduced to an amino group with subsequent cyclization, as shown in Scheme 2.109.



Scheme 2.109

Kinetics of the formation of 2-methoxycarbonyl-5,7-dinitrobenzothiazole-3-oxide by cyclization of *S*-(2,4,6-trinitrophenyl)mercaptoacetate in acetate, methoxyacetate, or *N*-methylmorfoline buffers has been studied [601]. In the first two buffers the cyclization follows two reaction pathways, which differ in the order of reaction steps, with the proton splitting off from the C–H group being the rate-limiting step in either pathway (Scheme 2.110).



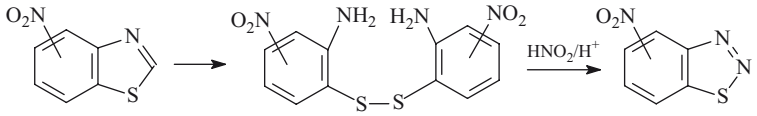
Scheme 2.110

In *N*-methylmorpholine buffer an increase in the concentration of the base results in a gradual decrease of the reaction order in the base and a change in the rate-limiting step of cyclization [601].

The synthesis, structure, and superoxide dismutase mimetic activity in vitro and the protection against reactive oxygen species in vivo of mononuclear copper complexes with 2-(4-methylphenylsulfamoyl)-6-nitrobenzothiazole have been reported [602].

Like 1,2,3-benzoxadiazoles, nitroderivatives of 1,2,3-benzothiadiazoles were obtained on diazotization of the corresponding *ortho*-aminothiophenoles [213, 218, 583]. The initial *ortho*-thiophenols for this reaction were synthesized by nucleophilic substitution of halogen in *ortho*-halogenoanilines. It turned out that 4-nitro- and

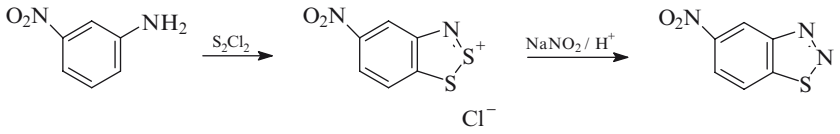
6-nitrobenzothiazoles on boiling with hydrazine in ethanol transformed to the corresponding disulfides, which form 4- or 6-nitro-1,2,3-benzothiadiazoles under the effect of nitrous acid (Scheme 2.111) [214].



Scheme 2.111

An attempt to synthesize 5- or 7-nitro-1,2,3-benzothiadiazoles in this way was unsuccessful. *meta*-Nitroaniline reacts with sulfur monochloride (Herz's reaction), while 1,2,3-benzothiazathiolium chloride reacts with nitrous acid to give a small amount of 5-nitro-1,2,3-benzothiadiazole, according to Scheme 2.112 [218, 603].

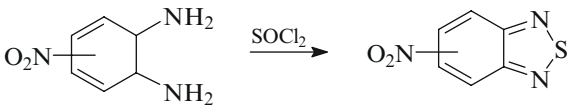
Different derivatives of 2,1,3-nitrobenzothiadiazole (earlier called nitropiazthiole)



Scheme 2.112

are obtained in the reaction between thionylchloride and the corresponding 1,2-diaminobenzenes [220, 223, 231, 246, 604–607]. Some of them, in particular, 4-nitro-2,1,3-benzothiadiazole (and also 4-nitro-2,1,3-benzoselenodiazole-nitropiazselenols) are effective against fungus diseases of cotton plants and grapes (Scheme 2.113) [607].

Sulfinylaniline [605, 608] or sulfur monochloride [609] can be used as cyclizat-

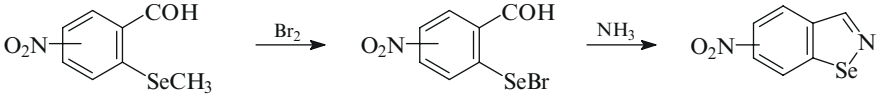


Scheme 2.113

ing agents. The formation of 5-nitro-2,1,3-benzothiadiazole in the reaction of 2,4-dinitroaniline with sulfur monochloride has been observed. Here, the reduction of substrate to 4-nitro-1,2-diaminobenzene followed by cyclization takes place [609].

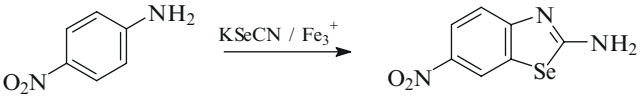
Nitrobenzisoselenazoles, Nitrobenzoselenazoles, and Nitrobenzoselenodiazoles

Analogously to the formation of 5-nitrobenzisothiazole [173], 5- and 7-nitrobenzisoselenazoles can be obtained in the reaction of 3- or 5-nitro-2-methylselenobenzaldehyde with bromine and ammonia (Scheme 2.114) [163].



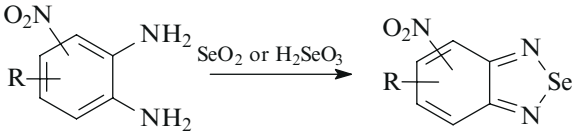
Scheme 2.114

para-Nitroaniline reacts with potassium selenocyanate in the presence of iron (III) salts to form 2-amino-6-nitrobenzoselenazole (Scheme 2.115) [610].



Scheme 2.115

The reaction of selenium dioxide or selenic acid with nitro-1,2-diaminobenzenes leads to the corresponding nitro-2,1,3-benzoselenodiazoles (Scheme 2.116) [223, 243, 244, 246, 366, 607, 611–620].



R = H, Alk, OAlk, Hal, Aryl

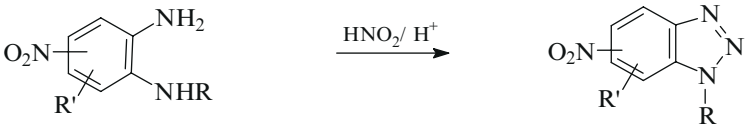
Scheme 2.116

In the literature [615–619] there are the results of quantitative investigations into the reaction of complex formation of H_2SeO_3 and aromatic *ortho*-diamines, –R–$C_6H_3(NH_2)_2$, which allow an accurate determination of the composition of the mixture at any pH, which is widely used in analytical chemistry of selenium.

Nitrobenzotriazoles

The most common and convenient way of obtaining nitro-1(*H*)-benzotriazoles is the condensation of nitro-1,2-phenylendiamines with nitrous acid [251, 252, 256,

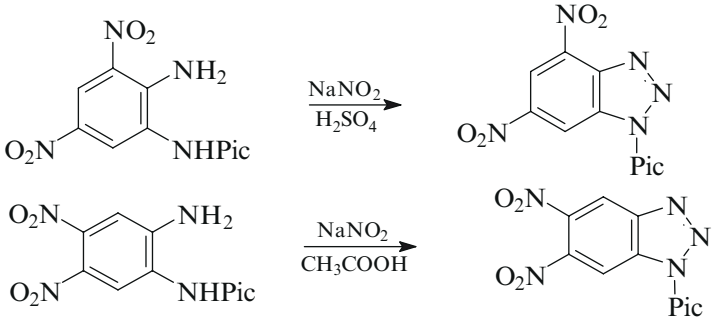
259–265, 342, 365, 366, 620–622]. In most cases this reaction is undertaken in the medium of hydrochloric acid or lower carboxylic acids – HCOOH, CH_3COOH (Scheme 2.117).



R = H, Alk, Ar, OH, OAlk, Het, SO_2Alk, SO_2Ar', R' = Alk, OCH_3

Scheme 2.117

High-energy materials such as 4,6-dinitro-1-(2′,4′,6′-trinitrophenyl)- and 5,6-dinitro-1-(2′,4′,6′-trinitrophenyl)benzotriazole have been obtained by treating the corresponding *ortho*-phenylenediamines with sodium nitrite in sulfuric and acetic acids, respectively (Scheme 2.118) [623].



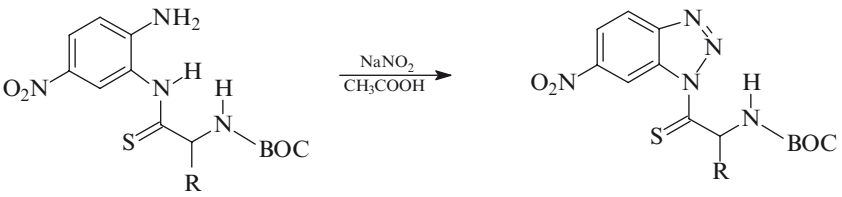
Scheme 2.118

The derivatives of nitrobenzotriazole α-aminothionic acids, used as thioacylating agents in the synthesis of thiopeptides and nitrobenzotriazole thioacylating reagents, have been obtained in a similar way (Scheme 2.119) [624, 625].

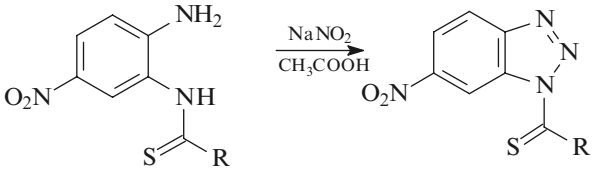
Thioanilides are treated with sodium nitrite either in the medium of glacial acetic acid or in 70% acetic acid to form the corresponding nitrobenzotriazoles in good yield (72–83%). In general terms, the stability of nonbenzenoid thiocarbonylbenzotriazoles is poor. Rapoport [624, 625] obtained aliphatic nitrated thiocarbonylbenzotriazoles. Probably, the electron-withdrawing nitro group in the benzotriazole ring improves the stability and allows isolating aliphatic thiocarbonylbenzotriazoles.

Following this method, the Katritzky team has prepared several novel aliphatic and aromatic thiocarbonyl-1*H*-6-nitrobenzotriazoles, as shown in Scheme 2.120 [5].

Interaction of 4-nitro-1,2-phenylendiamines with the respective acid chlorides gave regioselectively amides (83–99%). Resonance and inductive effect of the nitro group lowered the nucleophilicity of the amino group in the *para*-position, leaving

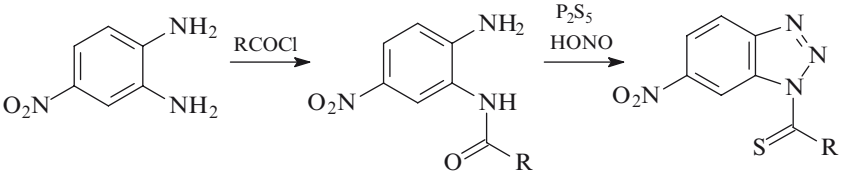


R = CH_3, CH_2Ph, $CH(CH_3)_2$, CH_2OBn, $CH_2CO_2CH_3$, $CH_2CO_2Bu^t$



R = $CH(OAc)CH_2CO_2CH_3$, $CH(OAc)Ph$, $CH{=}CHCO_2CH_3$—
$CH{=}CHCH_3$, $CH{=}CH_2$, $CH{=}CHPh$

Scheme 2.119



Yeilds of thiocarbonyl-1*H*-6-nitrobenzotriazoles (R, %)

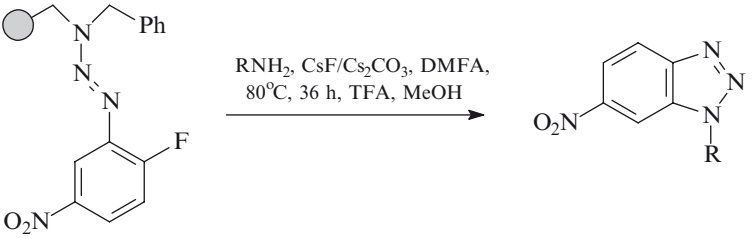
R	%	R	%
ethyl	84	4-methoxyphenyl	86
4-methylphenyl	98	4-bromophenyl	99
2-furanyl	95	pentyl	81
4-nitrophenyl	83	2-thienyl	91

Scheme 2.120

the *meta*-amino group to attack the carbonyl of acid chloride. Intermediated amides were converted to thiocarbonyl-1*H*-6-nitrobenzotriazoles crude yields by stirring at room temperature with phosphorus pentasulfide [5].

Benzotriazoles including nitrobenzotriazoles have been widely utilized by the research group of Katritzky as a synthetic auxiliary in a multitude of reactions [5, 626]. Benzotriazole is an inexpensive, stable, and biologically active compound, which can be easily introduced into organic molecules. The benzotriazole ring is extremely stable, and only rarely was ring cleavage encountered to give mostly products of nitrogen extrusion [626].

1-Alkyl-5-nitro-1*H*-benzotriazoles in excellent yield (90%) and purities (95%) were obtained, as illustrated in Scheme 2.121 [627].

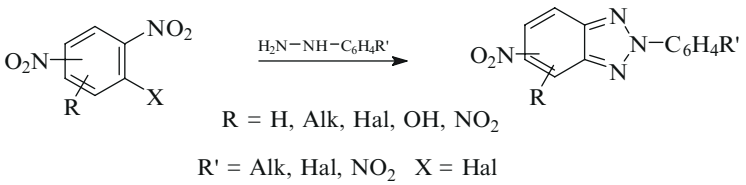


Scheme 2.121

Commercially available 2-fluoro-5-nitroaniline was diazotized and coupled to benzylaminomethylpolystyrene to give the immobilized triazene. After nucleophilic displacement with primary amines to furnish an aniline resin, the cleavage with trifluoroacetic acid in dichloromethane proceeded smoothly at room temperature within minutes, resulting in nitrobenzotriazoles [627].

4-Nitrobenzotriazole possessing an excellent herbicidal activity [628] has been prepared on oxidizing 2-acetylamino-6-nitrophenylhydrazine with chlorine [522]. *N*-Chloro derivative of 4-nitrobenzotriazole is used as an oxidizer of alkylamines [629]. 1-Acetyl-4-nitrobenzotriazole is the excellent selective *N*-acetylation agent for nucleosides [630].

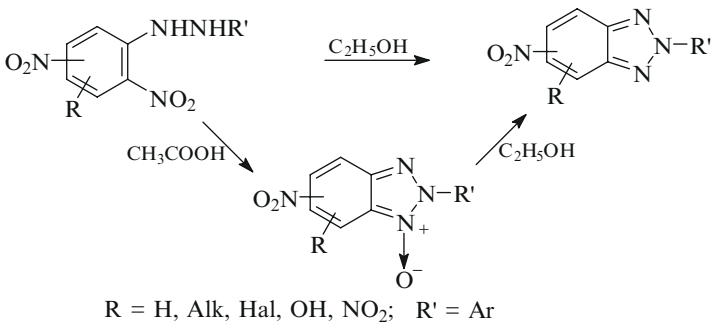
The most widely accepted way to the synthesis of 2*H*-benzotriazole nitroderivatives is the condensation of *ortho*-substituted halogenodinitro- or halogenopolynitrobenzenes with phenylhydrazine (Scheme 2.122) [260, 265, 271, 631–641].



Scheme 2.122

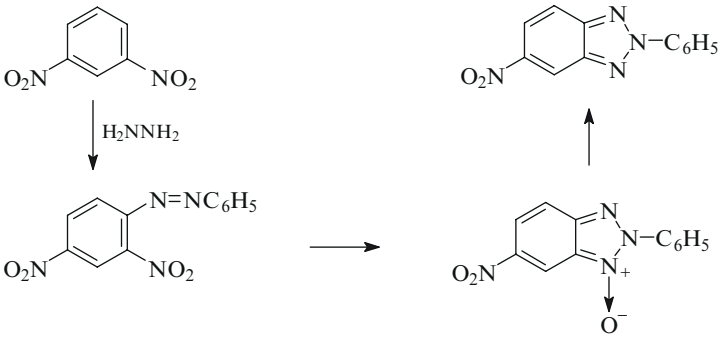
The initial stage of this reaction involves a nucleophilic halogen substitution followed by intermolecular redox cyclization of *ortho*-nitrohydrazobenzenes [642]. Instead of halogen the substrate can contain another group (NO_2, OAlk) [643–645]. It has been shown that in ethanol the aforementioned reaction proceeds with the formation of 2*H*-benzotriazole nitro derivatives, whereas in acetic acid their *N*-oxides are formed and, when boiled in ethanol, turn into the final products (Scheme 2.123) [637, 638, 646].

The reduction of 2,4-dinitroazobenzene by hydrazine in ethanol to 6-nitro-2-phenylbenzotriazole has been carefully studied [647]. The authors have proved that it goes via the formation of two intermediate products, that is, 2,4-dinitrohydrazobenzene



Scheme 2.123

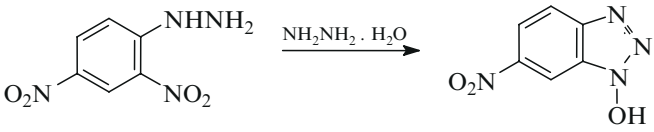
and 6-nitro-2-phenylbenzotriazol-1-oxide, which is obtained from the former as a result of cyclization (Scheme 2.124).



Scheme 2.124

The reaction of cyclization of 2,4-dinitrohydrazobenzene is described with a first order kinetic equation. The reaction rate depends on the pH value. In the pH range of 6.5–9.5 the rate constant is linearly dependent on the concentration of OH^- ions.

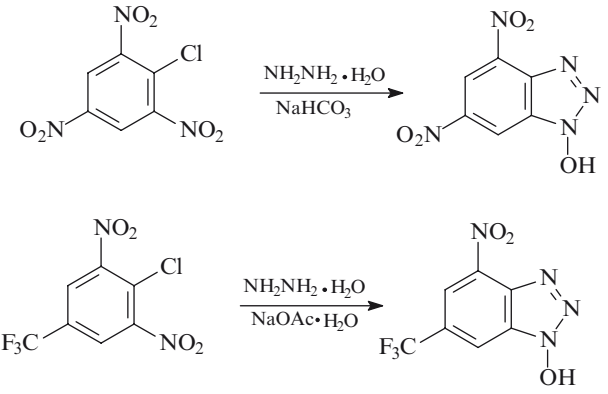
Synthesis of 1-hydroxy-6-nitrobenzotriazole from 2,4-dinitrophenylhydrazine has been described (Scheme 2.125) [647].



Scheme 2.125

1-Hydroxy-4,6-dinitrobenzotriazole [648, 649] and 1-hydroxy-4-nitro-6-trifluorome-thylbenzotriazole [649] have been synthesized in a similar manner. Later [650], an improved synthesis of these compounds from the corresponding

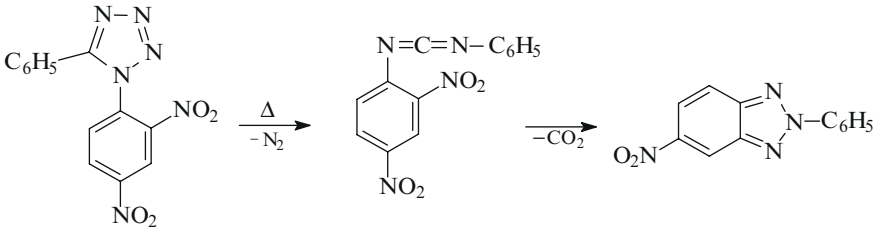
chlorinated nitrobenzenes with excess hydrazinium hydrate has been proposed (Scheme 2.126).



Scheme 2.126

The melting points of these compounds are significantly higher than those of compounds obtained by the method described in reference [649].

1-(2,4-Dinitrophenyl)-5-phenyltetrazole on heating turns to 2-phenyl-5-nitrobenzotriazole according to the Scheme 2.127 [392, 651].



Scheme 2.127

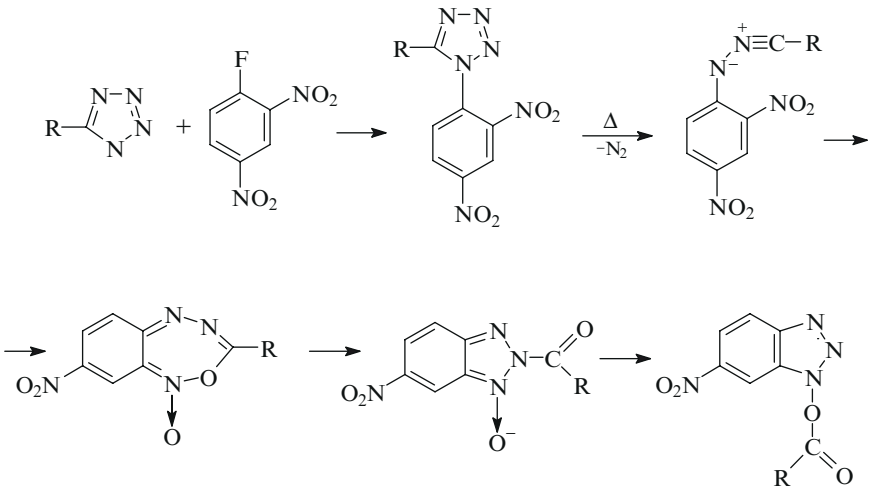
At the same time, the pyrolysis of its isomeric 2-substituted tetrazole results in 1-aroyloxy-6-nitrobenzotriazoles, as demonstrated in Scheme 2.128 [652].

4-Azobenzofuroxanes undergo intermolecular rearrangement to form 2-aryl-7-nitrobenzotriazoles (Scheme 2.129) [522].

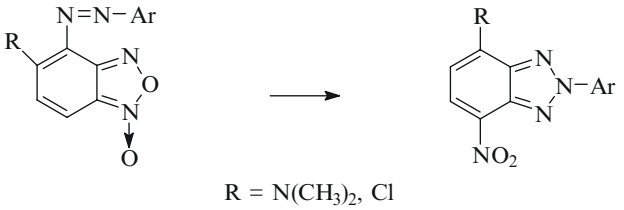
2-Aryl-4,7-dinitrobenzotriazoles are formed as a result of two rearrangements as shown in Scheme 2.130 [653].

The second transformation is a version of the aforementioned Boulton–Katrizky rearrangement [522]. Benzofuroxan was not isolated but appeared as an intermediate on heating 2,6-dinitro-3-azidoaryldiazenobenzene. The reaction starts with nucleophilic attack of the diazene fragment on the furoxan cycle nitrogen atom [653].

2,5-Diamino-4-nitroazobenzene turns into 2-phenyl-5-amino-6-nitrobenzotriazole in the presence of copper sulfite [654].

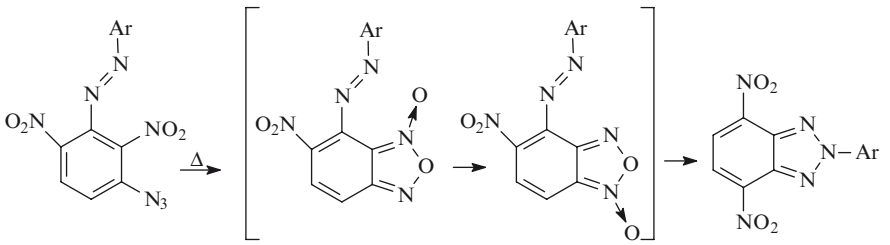


Scheme 2.128



R = $N(CH_3)_2$, Cl

Scheme 2.129

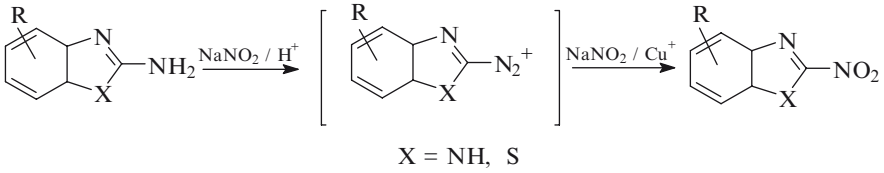


Scheme 2.130

Other Methods of Synthesis

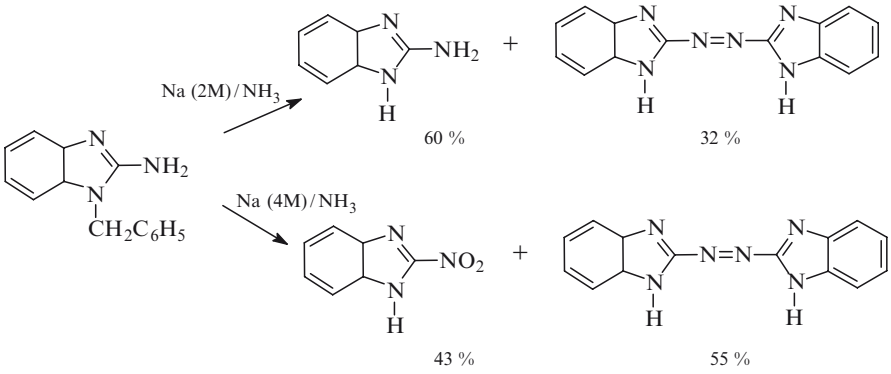
The Sandmeyer Reaction

The main method of introducing the nitro group into the benzazole cycle position 2 is Sandmeyer reaction (Scheme 2.131) [655–658].



Scheme 2.131

Pozharskii and his colleagues have established that 1-benzyl-2-aminobenzimidazole in liquid ammonia in the presence of metallic sodium turns into 2-nitrobenzimidazole and 2,2′-azobenzimidazole, as shown in Scheme 2.132 [659–661].



Scheme 2.132

The first stage of this unusual reaction involves debenzylation of the substrate to form 2-aminobenzimidazole polyaniones. The formation of 2,2′-azobenzimidazolone is the result of autooxidation of 2-aminobenzimidazole di- and trianiones, when 2-nitrobenzimidazole is formed on oxidizing of radical anions [660].

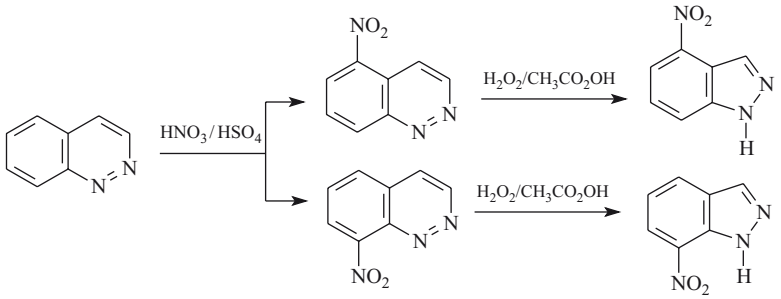
Recyclization

It is known that 5- and 8-nitrozinecolynes are oxidized to 4-nitro- and 7-nitroindazoles, respectively, by hydrogen peroxide in acetic acid (Scheme 2.133) [662].

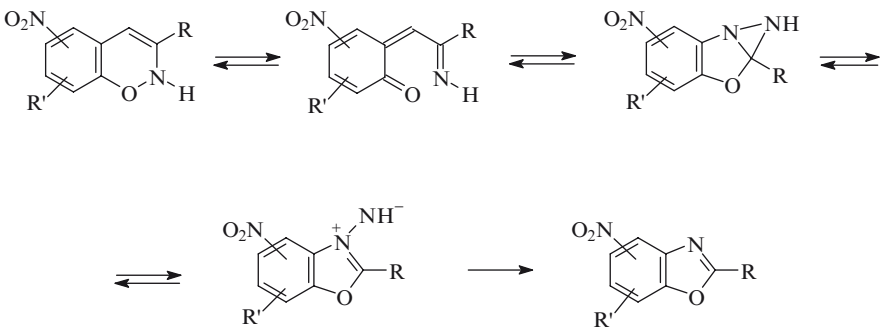
This is the way the synthesis of 4-nitro[3-^{14}C]- and 7-nitro[3-^{14}C]indazole has been performed [662].

A possible mechanism of the recyclization of 1,2,4-benzoxadiazones to form the corresponding benzoxazoles has been described, as illustrated in Scheme 2.134 [663].

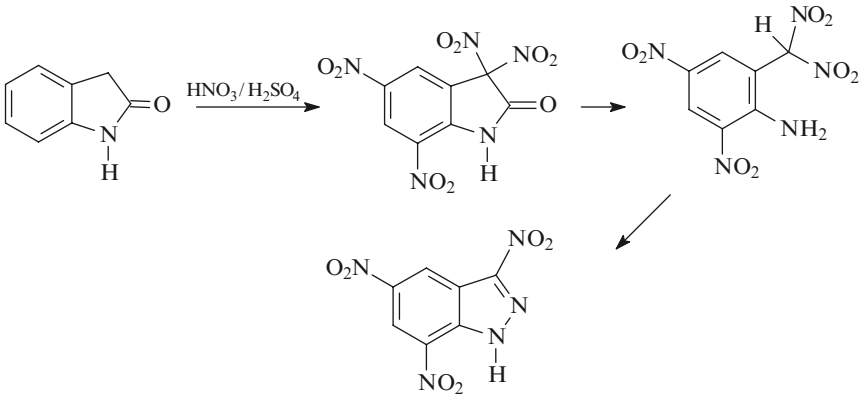
The nitration of oxyindole leads to 3,3,5,7-tetranitrooxindole, which transforms with ring-opening and undergoes decarboxylation to form 4,6-dinitro-2-(dinitromethyl)aniline. The latter is cyclized into 3,5,7-trinitroindazole [664]. The mechanism of ring transformation leading to nitroindazole is not clear yet and needs detailed examination (Scheme 2.135).



Scheme 2.133

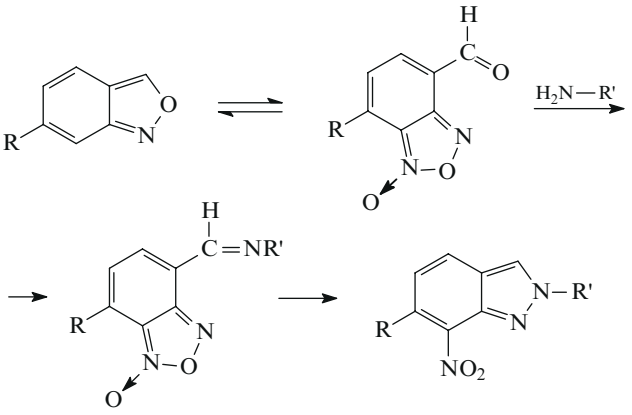


Scheme 2.134



Scheme 2.135

Interconversions of nitroanthranils equilibrated on heating with benzofurazan *N*-oxides lead to the formation of the corresponding nitroindazoles (Scheme 2.136) [665, 666].

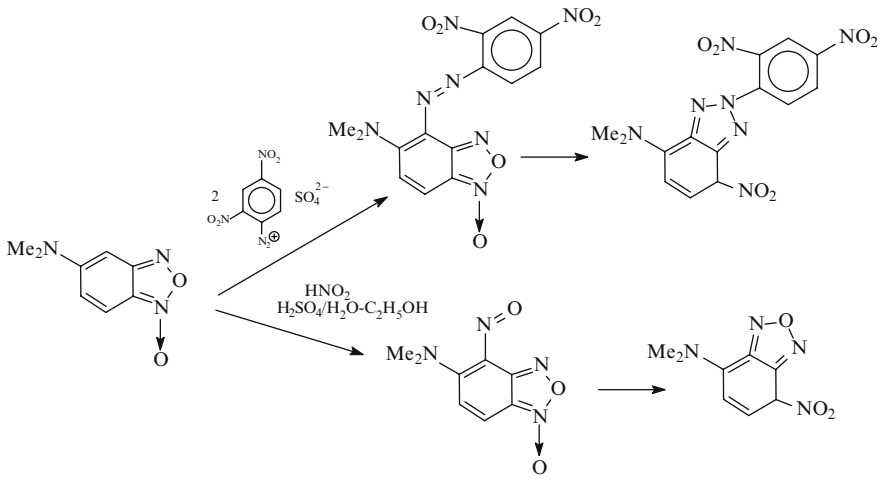


R = H, OMe, Cl; R' = Alk, Ph, CH_2Ph, OAlk, OPh, OCH_2Ph, NMe_2, NHPh

Scheme 2.136

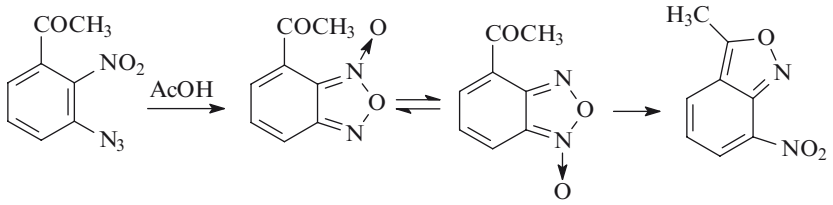
Selective reduction of nitrobenzothiazole *N*-oxides makes it possible to synthesize nitrobenzothiazoles, which so far were difficult or inaccessible to prepare [667–670].

Nitrated benzotriazole and benzofurazan were obtained as a result of an interesting rearrangement in the reaction of 5-dimethylaminobenzofuroxan with 2,4-dinitrobenzenediazonium sulfate or with HNO_2 in H_2SO_4/H_2O-C_2H_5OH (Scheme 2.137) [671].



Scheme 2.137

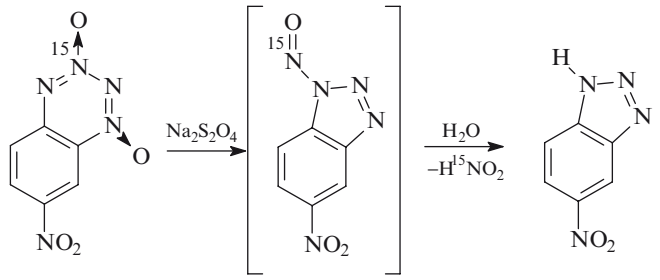
Similarly, heating of 2-NO_2-3-N_3-$C_6H_3COCH_3$ in AcOH to 120° gave nitroanthranyl and not the intermediate benzofuroxan system, as shown in Scheme 2.138 [671].



Scheme 2.138

4,6-Dichloro-5,7-dinitrobenzofuroxan was transformed to 4,6-dichloro-5,7-dinitrobenzofurazan by PPh_3 polymer support [672].

5(6)-Nitrobenzotriazole was obtained by reduction of benzo-1,2,3,4-tetrazine 1,3-dioxides (BTDOs) with $Na_2S_2O_4$ or $SnCl_2$ via intermediate *N*-nitrosobenzotriazoles (Scheme 2.139) [162].



Scheme 2.139

The ^{15}N-labeling experiments have shown that the ^{15}N-3-labeling atom of N →O fragment of the tetrazine ring is incorporated into the nitroso group of benzotriazole. The authors [162] have suggested the biological activity of BTDOs to be due to their ability to release nitrosating species, that is, *N*-nitrosobenzotriazole, in the course of reduction.

It has already been shown that the nitration with nitric acid in acetic anhydride provides the general way of obtaining *N*-nitroheterocycles. As an alternative synthesis of the aforementioned compounds, and, in particular, 1-nitrobenzotriazole, the reaction of 1-chlorobenzotriazole with the silver nitrate–triphenylphosphite complex can be suggested [273].

Conclusions

The azoles occupy an important place in the chemistry of heterocyclic compounds. Their unique properties and specific biological activity attract much attention of scientists worldwide. A much used and convenient method for the preparation of

nitroazoles is the electrophilic nitration. Electrophilic substitution reaction of azoles and benzazoles is a complex process in which the experimental conditions can modify the product orientation. The ability of azoles to electrophilic substitution is determined by the activity of reagents, the basicity of substrates, and the acidity of medium. The existence of an annelated benzene ring in the benzazole molecule influences much of its ability for electrophilic substitution – all benzazoles are more easily nitrated than their five-membered analogs, and the nitro group is generally introduced into the arylene fragment of the molecule.

The nitration of benzazoles is usually effected using concentrated (65%) to fuming (100%) nitric acid generally at temperature between 0 and 5°C. Indazoles are usually nitrated into 5 position, benzimidazoles – as a rule – into 5- or 6-position of the phenylene fragment whereas benzotriazole into position 4 or 7. For the preparation of other nitrobenzazoles the reaction of heterocyclization is used.

The nitroazoles are widely used in the reaction of vicarious nucleophilic substitution of hydrogen. Vicarious nucleophilic *C*-amination is, practically, the single method of direct introduction of the amino group into nitro compounds. Using the vicarious nucleophilic substitution reaction we have successfully carried out the *C*-amination of some representatives of nitrobenzazoles, nitroazoles, and model compounds thereof and studied the structure of aminated products and the *C*-amination mechanism [673–678].

Recently, the investigations of nitrobenzisoxazoles mainly 6-nitrobenzisoxazole-3-carboxilate ions have received considerable interest due to their participation in reverse micellar systems [679–682]. Reverse micelles are of considerable interest as reaction media because they are powerful models for biological compartmentalization, enzymatic catalysis, and separation of biomolecules. Solutions of ionic surfactants in apolar media may contain reverse micelles, but they may also contain ion pairs or small clusters with water of hydration [679]. Molecular design of nonlinear optical organic materials based on 6-nitrobenzoxazole chromophores has been developed [451].

The polynitrobenzazoles are adequate precursors for the preparation of high-energy compounds. The investigations in the field of polynitro annelated azoles – dinitrobenzimidazoles [683], 4,6-dinitrobenzisoxazoles [684], 4,6-dinitrobenzisothiazoles [685], 4,6-dinitro-2,1,3-benzothiadiazole, 4,6-dinitrobenzo-2,1,3-selenadiazole, 4,6-dinitrobenzotriazoles [686], 4,6-dinitrobenzofurazans [686, 687], 4,6-dinitrobenzofuroxans [686, 688–692] – have great future prospect.

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