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Direct Functionalization of C–H Fragments in Nitroarenes as a Synthetic Pathway to Condensed N-Heterocycles

Svyatoslav Shevelev and Alexey Starosotnikov

Abstract The paper consolidates the data published on the synthetic pathways to condensed N-heterocycles via direct functionalization of C–H fragments in nitroarenes in the *ortho*-position relative to the nitro group.

Keywords Cycloaddition reactions · Nitroarenes · Nitrogen heterocycles · S_N^H reactions

Contents

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1 Introduction

Nitrogen heterocycles represent one of the most important classes of organic compounds. Found in nature or synthesized, they have gained wide appreciation as pharmaceuticals or dyes. Despite the extensive achievements done in this field, the development of novel synthetic methods for the preparation both of the known compounds as well as of their analogues, which may possess better properties or a considerably higher biological activity, seems to be a promising research task. There is also a growing fundamental interest in the synthesis of new heterocyclic systems. This is evidenced by a number of reviews and monographs on the synthesis, chemical, and biological properties of nitrogen heterocycles that have been published over the last decade [1–4].

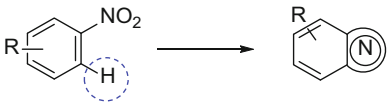
In this review, we consider aromatic nitro compounds (nitroarenes) with the vacant *ortho*-position relative to the nitro group, as a basis for the synthesis of condensed nitrogen heterocycles (benzo-annelated N-heterocycles) (Scheme 1).

Nitroarenes is a class of aromatic compounds, which are known to possess a dual reactivity. Indeed, an aromatic nitro group activates the carbon atoms located in the *ortho*- and *para*-positions of the benzene ring towards a nucleophilic attack. When a good leaving group is present in one of these positions, the nucleophilic *ipso*-substitution takes place. Aromatic nucleophilic substitution (S_N^{Ar}) is well established to be a two-step process, which involves a nucleophilic addition at the carbon atom bearing a leaving group (σ^{ipso}-adduct formation) and departure of a nucleofuge. Further formation of a heterocyclic ring is possible either via cyclization with participation of the nitro group or through displacement of the latter (it should be noted that the nitro group itself is a good leaving group as well) (Scheme 2).

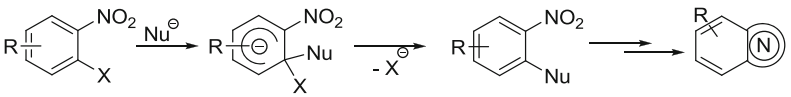
On the other hand, if hydrogen atoms occupy the *ortho*-positions relative to the nitro group, a nucleophile addition might also result in the formation of anionic σ^H-complexes. However, their further transformations are hampered because the hydride ion (a formal leaving group) is a thermodynamically unstable particle not prone to solvation. Moreover, the energy of the C–H bond is rather high. Therefore, the intermediate σ^H-complexes can be converted into aromatic compounds (S_N^H product) either by means of oxidation (oxidative nucleophilic substitution of hydrogen, ONS) or through elimination of HX, provided a leaving group X is present in the nucleophilic reagent (vicarious nucleophilic substitution of hydrogen, VNS) (Scheme 3).

Another important feature is that the nitro group is an electron-withdrawing substituent, increasing electrophilicity of an aromatic system. Due to this fact, nitroarenes sometimes exhibit the reactivity, which is similar to that of conjugated nitroalkenes, and are able to undergo pericyclic reactions (Scheme 4).

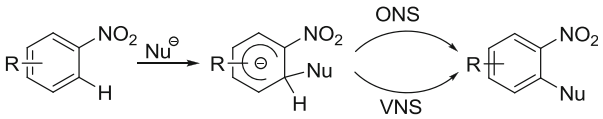
In the following sections of this chapter, we will consider some other possibilities for the formation of heterocyclic compounds by using functionalization of C–H fragments in nitroarenes.



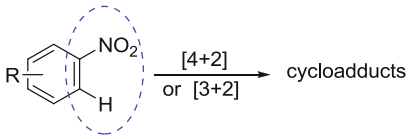
Scheme 1 Nitroarenes with unsubstituted *ortho*-position as a basis for the synthesis of N-heterocycles



Scheme 2 Nucleophilic *ipso*-substitution in nitroarenes



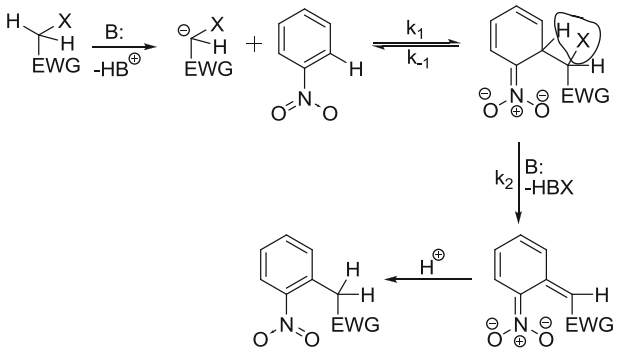
Scheme 3 S_N^H reactions of nitroarenes



Scheme 4 Cycloadditions to nitroarenes

2 Synthesis of Condensed N-heterocycles via Nucleophilic Substitution of Hydrogen (S_N^H) in Nitroarenes

The S_N^H methodology is currently recognized as one of the most efficient synthetic tools for functionalization of aromatic and heteroaromatic compounds. In particular, the S_N^H reactions allow one to annelate a heterocyclic ring to π-deficient arenes and hetarenes [5–7]. An obvious advantage of this strategy is that there is no need to introduce a leaving group into the molecule of the starting material (as in the case of nucleophilic *ipso*-substitution), because a nucleophilic attack takes place at the unsubstituted carbon atom of a (hetero)aromatic system. For this reason, it is the aromatic substrate that must be activated. Carbocyclic aromatic compounds are usually activated by electron-withdrawing substituents, and, indeed, nitroarenes appear to belong to the family of the most activated aromatic systems. It should be noted that, in most cases, the S_N^H reactions are somewhat similar to S_N^{ipso}-substitutions; however, the formation of σ^H-complexes proceeds much faster than a similar reaction, leading to the σ^{ipso}-complexes. As a result, interaction of π-deficient



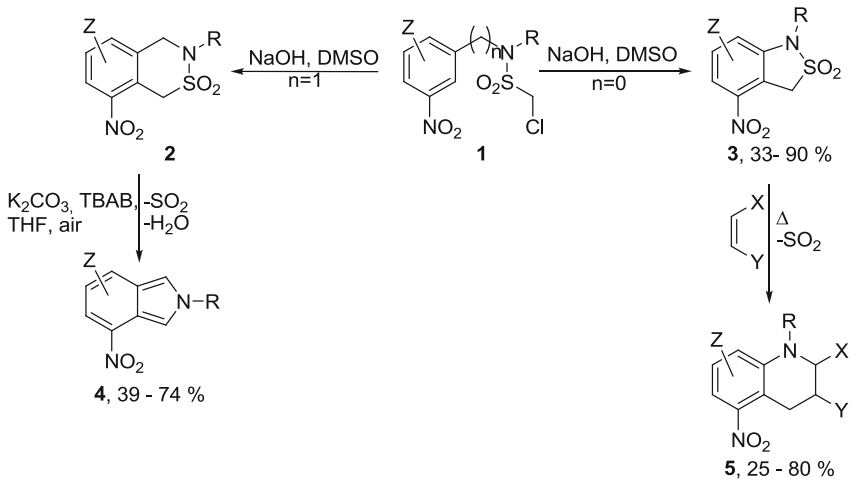
Scheme 5 Vicarious nucleophilic substitution of hydrogen (general scheme)

aromatic substrates with nucleophiles proceeds under rather mild conditions (at low temperature) in the presence of an excess of base, thus leading to substitution of hydrogen, whereas products of the displacement of good leaving groups can be obtained under more drastic conditions. Numerous examples of such transformations are summarized in the review articles [8–10].

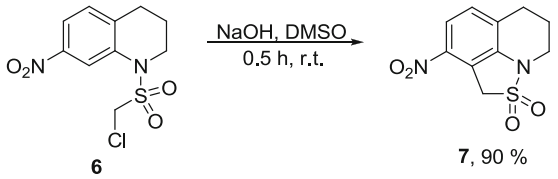
In this section, we will focus on two main approaches to the synthesis of condensed N-heterocycles based on nitroarenes using the S_N^H methodology: vicarious nucleophilic substitution of hydrogen (VNS) and oxidative nucleophilic substitution of hydrogen (ONS).

2.1 *Vicarious Nucleophilic Substitution of Hydrogen*

The concept of vicarious nucleophilic substitution of hydrogen in electron-deficient arenes was originally developed at the beginning of 1980s by M. Makosza and co-workers, and since then has been thoroughly elucidated [11, 12]. The reaction is initiated by fast and reversible addition of carbanion, bearing a leaving group X (e.g., halogen), to nitroarene, followed by the base-induced β-elimination of H-X from the resultant σ^H-adduct (Scheme 5). At least two equivalents of the base are necessary to cause the reaction, one for deprotonation of CH acid, thus generating the corresponding carbanion, and the second one to induce the β-elimination of H-X. The last step is C-protonation of the nitronate intermediate leading to the substituted nitrobenzene (Scheme 5) [13–16]. It has been reported that the choice of solvent, the nature and concentration of the base, as well as the steric demands for the carbanion have considerable influence on the ratio of isomeric products [17]. When a high excess of the base is present, the H-X elimination does occur much faster than dissociation of the σ^H-adduct, and, as a result, the reaction becomes irreversible. A low reaction temperature and a high concentration of the base guarantee the reaction to proceed under kinetic control with irreversible formation of the σ^H-adduct (Scheme 5). Since the β-elimination of HX from the



Scheme 6 Synthesis of N-heterocycles on the basis of sultams



Scheme 7 Synthesis of tricyclic sulfonamides

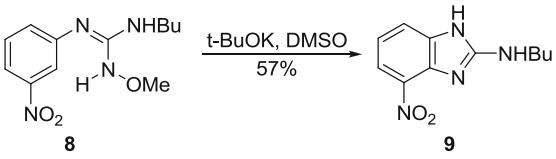
σ^H-adducts is much faster than the reverse reaction ($k_2[B] >> k_{-1}$) [18, 19], the ratio of products reflects the ratio of rate constants k_1 for the addition step.

The VNS process, as an attractive and convenient method for incorporation of alkyl-, amino-, or hydroxy groups in nitroarenes, was first reviewed in 1987 [12]. An interested reader may be referred to several reviews generalizing the data on the synthesis of fused nitrogen heterocycles (indoles, quinolines, purines, etc.) on the basis of VNS reactions [9, 20, 21].

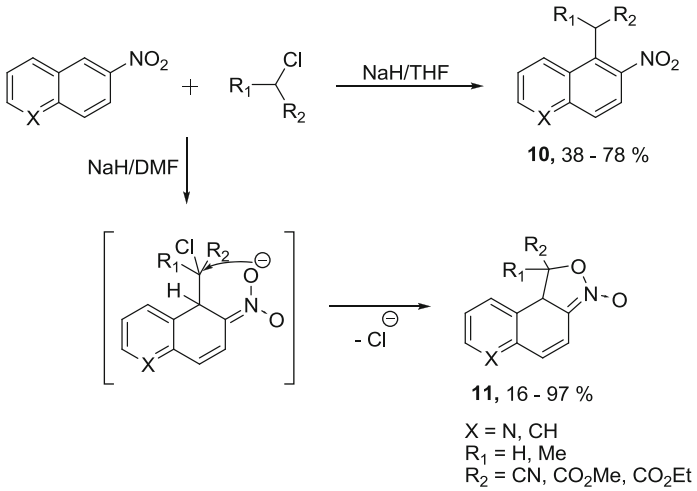
The formation of heterocycles by the VNS methodology has been shown to occur either by direct intramolecular VNS processes or through transformations of the *ortho*-nitrobenzyl derivatives resulting from intermolecular VNS reactions.

Scheme 6 exemplifies the first path. Intramolecular cyclization of sulfonamides **1** is caused by action of a base, thus resulting in the formation of nitroaromatics fused with five- or six-membered heterocycles [22–24]. It should be emphasized that in some cases the formation of isomeric products can be observed due to a nucleophilic attack at the *para*-position relative to the nitro group. Also it is worth noting that the cyclic sulfamides **2** and **3** can be used as precursors to obtain some other N-heterocyclic compounds, such as isoindoles **4** [25] or 1,2,3,4-tetrahydroquinolines **5** [24] (Scheme 6).

Another example of intramolecular VNS cyclization of sulfamides leading to *peri*-annelated heterocycles is shown in Scheme 7 [23].



Scheme 8 Synthesis of benzimidazole through the VNS reaction



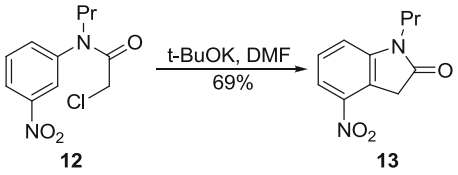
Scheme 9 Synthesis of benzo-fused cyclic nitronates

Treatment of guanidine **8** with a base in DMSO gives rise to 2-butylamino-4-nitrobenzimidazole **9** in 57% yield [26] (Scheme 8). In this case, the intramolecular VNS reaction proceeds exclusively at the *ortho*-position relative to the nitro group, while the methoxy group acts as a leaving group.

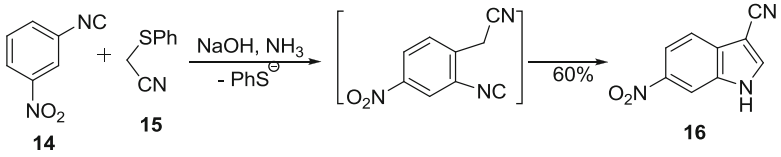
2-Nitronaphthalene and 6-nitroquinoline have been found to react easily with 2-chloronitriles and the corresponding esters in the presence of NaH [27] (Scheme 9). Depending on solvent, it is possible to obtain either VNS products **10** or cyclic nitronates **11**.

The authors have found that nitronates **11** are derived from intramolecular nucleophilic displacement of the chloro atom with oxygen of the nitro group (Scheme 9). Moreover, the intramolecular VNS reactions of nitroarenes proved to be a successful procedure for the synthesis of various indole derivatives. For instance, cyclization of 3-nitrochloroacetanilide **12** caused by action of *t*-BuOK affords N-substituted oxindole **13**, which is hardly accessible by other methods [28] (Scheme 10).

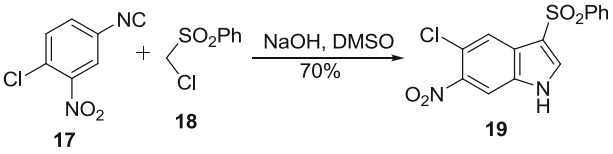
A number of publications deal with the use of nitroaryl isocyanides as direct precursors of nitroindoles. The starting isocyanides have been obtained by using the VNS reactions. Thus, in the reaction of 3-isocyanonitrobenzene **14** with



Scheme 10 Synthesis of 4-nitro-2-oxindole via the VNS cyclization



Scheme 11 VNS/isocyanide cyclization in the synthesis of indole **16**



Scheme 12 VNS/isocyanide cyclization in the synthesis of indole **19**

(phenylthio)acetonitrile **15**, the initial displacement of hydrogen is followed by the base-induced intramolecular cyclization, affording 3-cyano-6-nitroindole **16** in 60% yield [29] (Scheme 11).

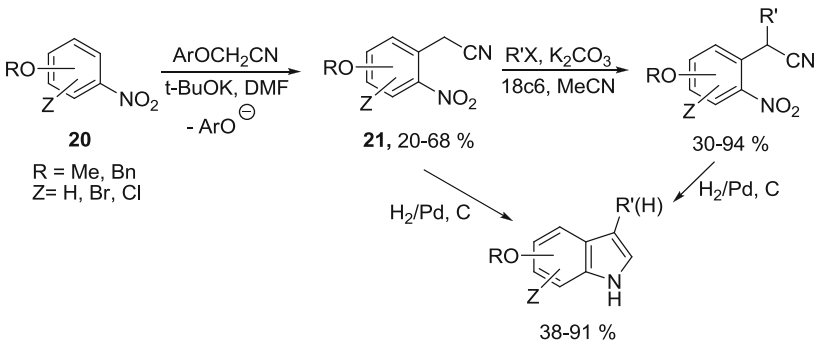
A similar reaction of compound **17** with phenyl(chloromethyl)sulfone **18**, as a vicarious nucleophile, affords 3-sulfonylindole **19** [29] (Scheme 12).

An easily occurring *ortho*-alkylation of nitroarenes under VNS conditions has allowed a convenient approach to indole derivatives hardly accessible by other methods.

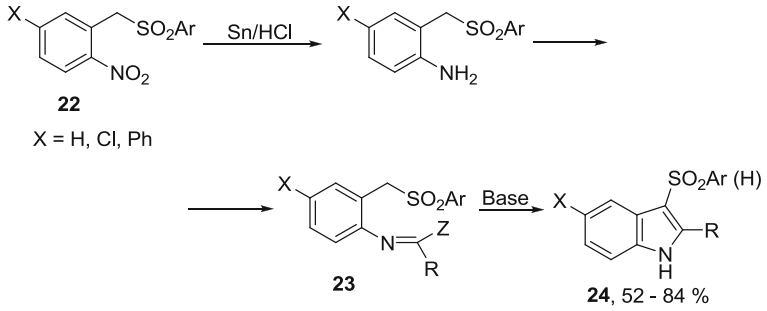
This approach is nicely illustrated by cyanomethylation of substituted nitrobenzenes **20** [30, 31], followed by hydrogenation of *ortho*-nitroacetonitriles **21** [32, 33] (Scheme 13).

Another approach deals with reduction of the nitro group in VNS products, such as sulfones **22**, their transformation into imines, isocyanides or imidates **23** which are prone to base-promoted cyclization into functionalized indoles **24** [34, 35] (Scheme 14).

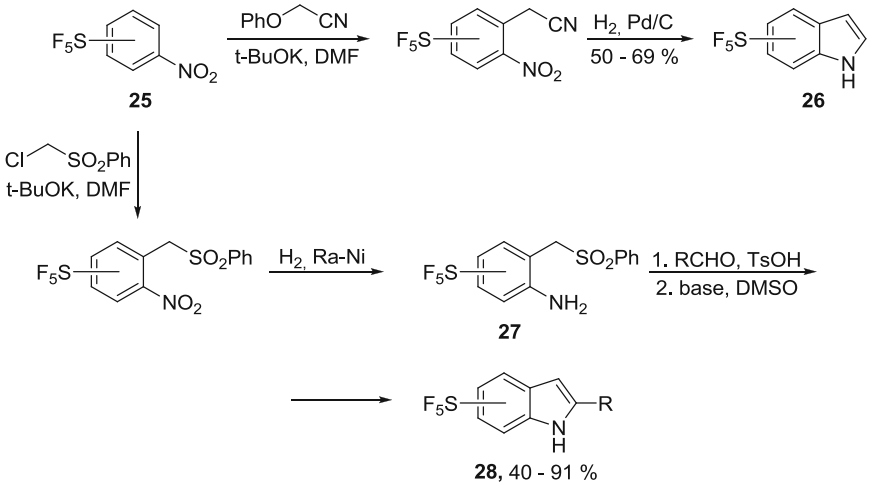
Both approaches described above have been used for the synthesis of indoles bearing the pentafluorosulfanyl group [36, 37]. The reaction of *meta*- and *para*-nitro (pentafluorosulfanyl)benzene **25** with phenoxyacetonitrile (Scheme 15) under VNS conditions followed by hydrogenation gave rise to SF_5-substituted indoles **26**. At the same time, the reaction of nitro compounds **25** with chloromethyl phenyl sulfone and the subsequent reduction of the nitro group in substitution products led to amines **27** - precursors of 2-substituted indoles **28** (Scheme 15).



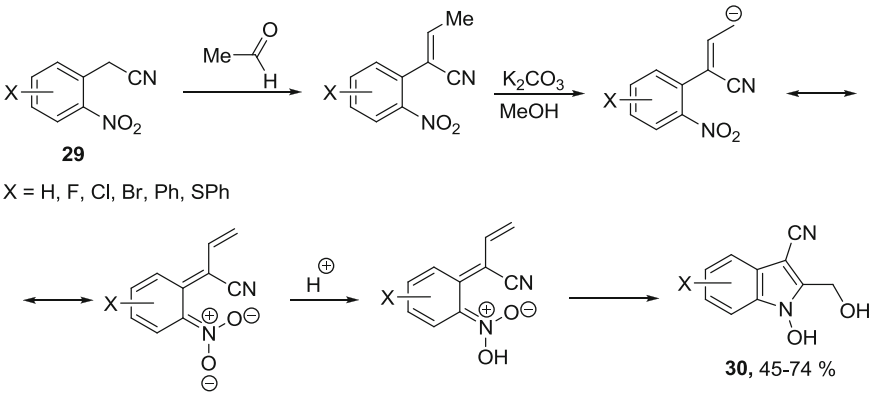
Scheme 13 Heterocyclizations of *ortho*-nitrophenyl acetonitriles



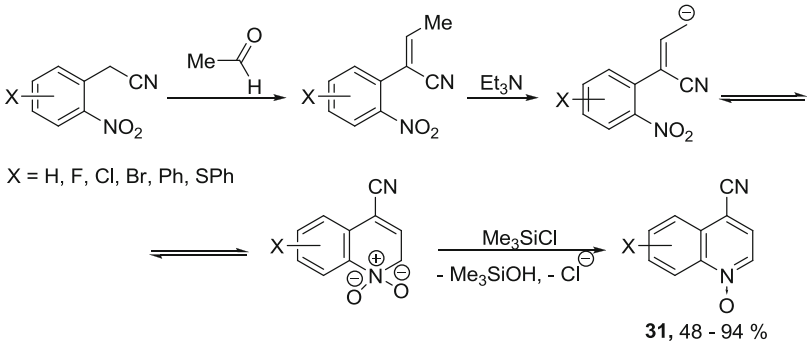
Scheme 14 Synthesis of 3-sulfonylindoles



Scheme 15 VNS approach to pentafluorosulfanyl-substituted indoles



Scheme 16 Synthesis of N-hydroxyindoles



Scheme 17 Synthesis of quinoline N-oxides

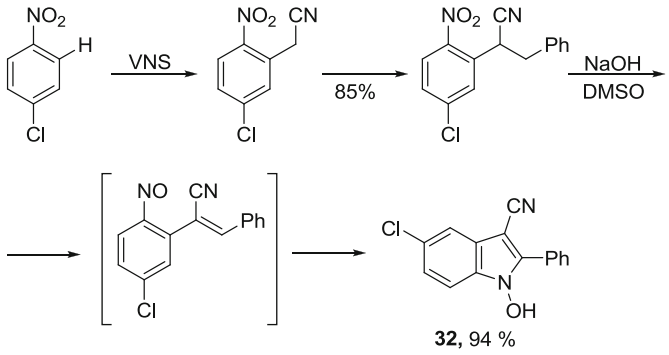
An aromatic nitro group sometimes participates in the formation of indoles, in particular of N-hydroxy derivatives. For example, the reaction of *ortho*-nitroaryl substituted acetonitriles **29** with acetaldehyde followed by treatment with K_2CO_3 afforded N-hydroxyindoles **30**, as the major products [38] (Scheme 16).

Use of other reagents for the cyclization step (i.e., Me_3SiCl/Et_3N) allowed quinoline N-oxide derivatives **31** to be obtained in high yields [38] (Scheme 17).

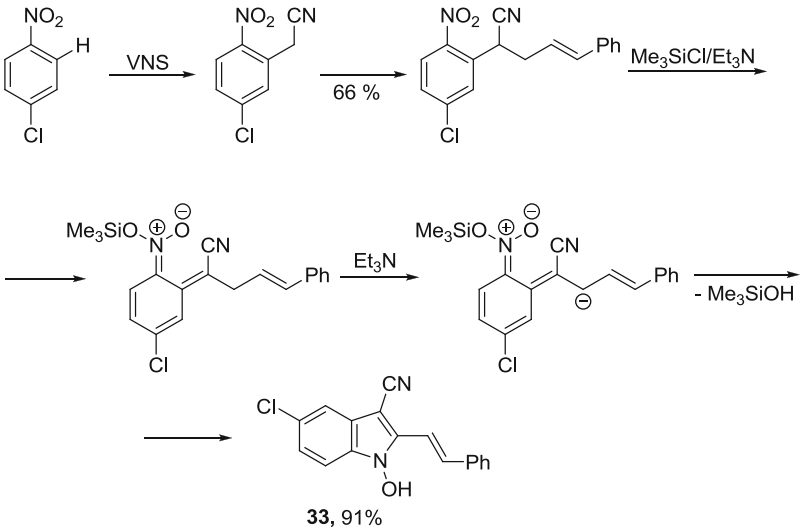
Polyfunctional N-hydroxyindole derivatives **32** have been synthesized by using the sequence of reactions, involving the VNS of hydrogen, alkylation, and base-catalyzed cyclization [39] (Scheme 18).

Use of Me_3SiCl/Et_3N system for the cyclization step in a similar reaction (Scheme 19) has also resulted in the formation of N-hydroxy indole **33** in high yield [40].

There are several synthetic pathways to benzo[*c*]isoxazoles (anthranils) based on application of the VNS methodology in nitroarenes. Dehydration of *ortho*-nitrobenzyl derivatives **34** by action of Me_3SiCl/Et_3N affords 3-substituted anthranils **35** [41] (Scheme 20).



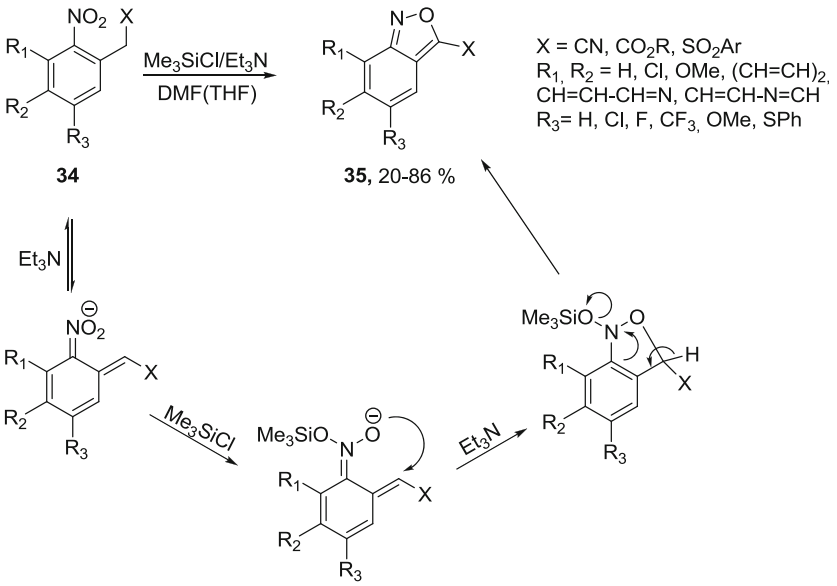
Scheme 18 Synthesis of N-hydroxy-substituted indoles



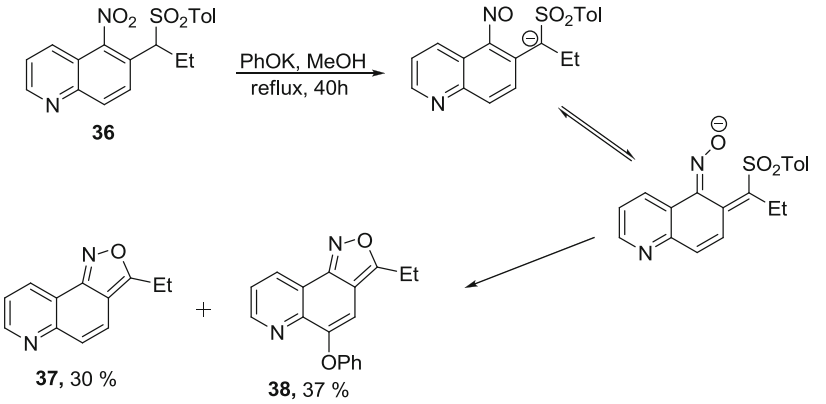
Scheme 19 Synthesis of N-hydroxy-substituted indoles

Besides, benzo[*c*]isoxazole derivatives were obtained when the VNS products derived from bicyclic nitroarenes were treated with potassium phenolate [42] or thiophenolate [43]. In case of 5-nitroquinoline **36** (Scheme 21) a mixture of two condensed isoxazoles **37** and **38** was obtained.

The VNS methodology has been reported to be effective for the synthesis of benzo-annelated six-membered N-heterocycles. Indeed, the reaction of *ortho*-nitrobenzyl sulfones **39** with diethyl maleate (or fumarate) takes place in the presence of K_2CO_3 under phase-transfer conditions to give quinoline N-oxides **40** [44] (Scheme 22).



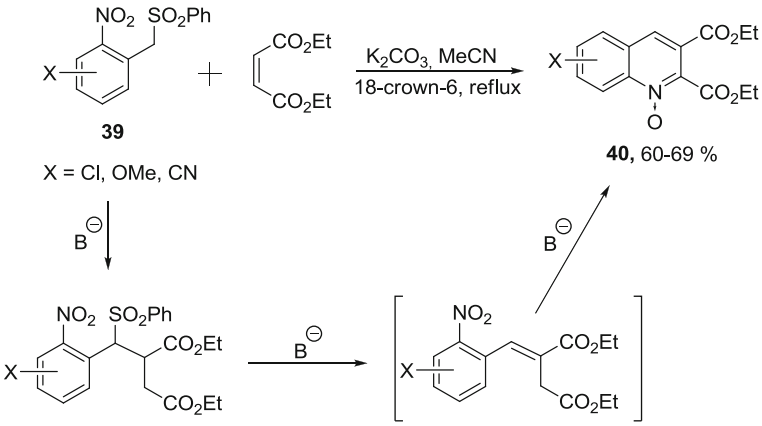
Scheme 20 Annelation of the isoxazole ring to *ortho*-nitrobenzyl derivatives



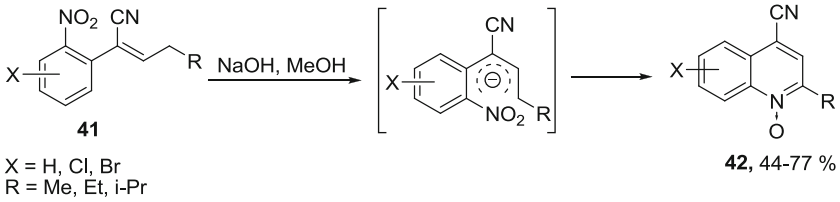
Scheme 21 Synthesis of isoxazoloquinolines

Compounds (**41**) derived from condensation of *ortho*-nitrobenzyl cyanides with aliphatic aldehydes can be transformed by action of base into 4-cyanoquinoline-1-oxides **42** [45] (Scheme 23).

A number of tricyclic heterosystems have been synthesized from nitroindoles and nitroindazoles [46, 47]. In these transformations the vicarious amination of bicyclic compounds **43** at the *ortho*-position relative to the nitro group proved to be the key step. 1,1,1-Trimethylhydrazonium iodide (TMHI) was used as the VNS-aminating agent (Scheme 24). Reduction of amines **44** followed by heterocyclization resulted in the formation of various types of heterocycles **45**–**48**.



Scheme 22 Synthesis of quinoline N-oxides

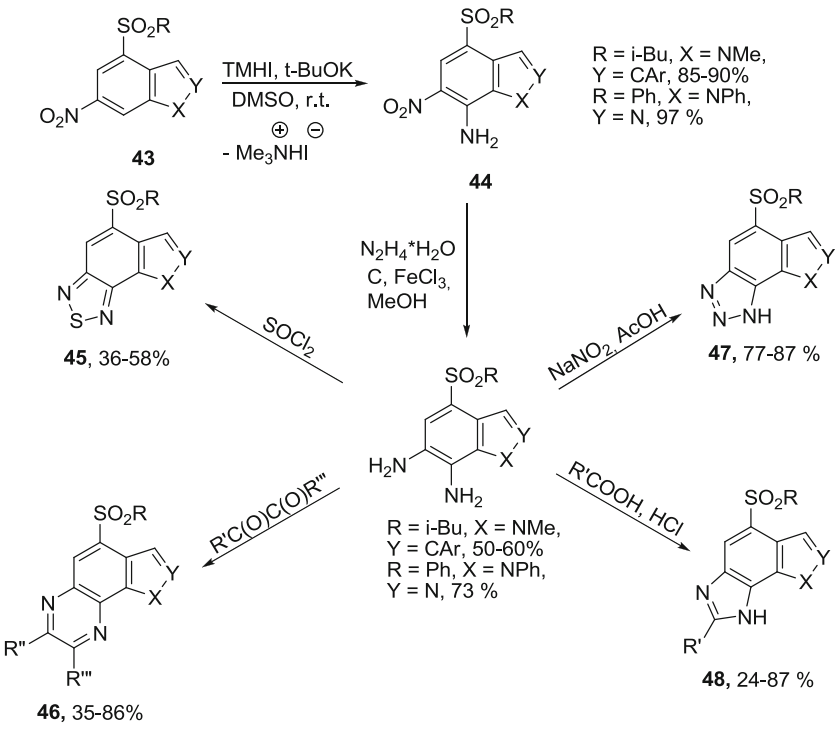


Scheme 23 Synthesis of quinoline N-oxides

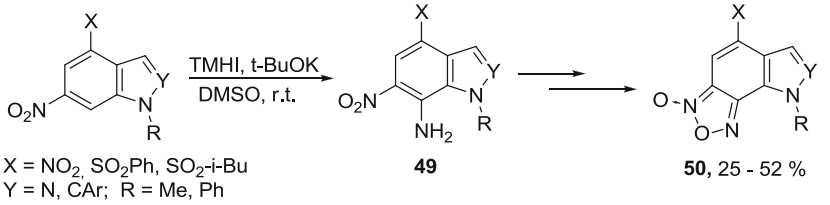
Nitroamines **44** as well as their analogues **49** were used for the synthesis of tricyclic furoxan derivatives **50** [46–48] (Scheme 25).

Benzo-annelated nitrogen heterocycles (indoles, quinolines, isoquinolines, etc.) are often found to be a part of biologically active compounds of both natural and synthetic origin. In a considerable body of data on the syntheses of these compounds, which have so far been documented in the literature, the crucial step is vicarious nucleophilic substitution of hydrogen in nitroarenes. Good examples are presented by the synthesis of nordehydrobufotenine [49], eupolauramine [50, 51], damirone [52], and aklavinone [53].

In conclusion, it is worth noting that the VNS methodology is now commonly recognized as a convenient and versatile synthetic tool to obtain a great deal of nitrogen-containing heterocycles from nitroarenes. The data presented in this section are not intended to be exhaustive ones. Availability of nitroarenes and a variety of substituents, which can be introduced into the core structures of nitroarenes by using the VNS reactions, provide an easy access to a wide range of nitrogen-containing heterocycles.



Scheme 24 Heterocyclizations of fused *ortho*-phenylenediamines

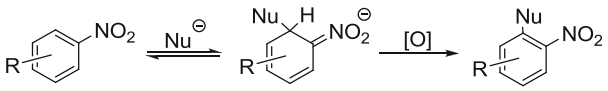


Scheme 25 Synthesis of condensed benzofuroxans

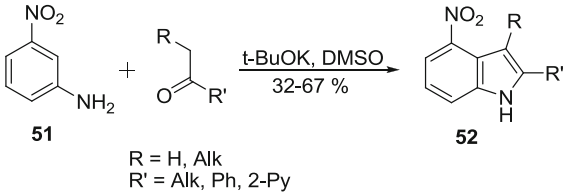
2.2 *Oxidative Nucleophilic Substitution of Hydrogen*

Another important type of the S_N^H processes is oxidative nucleophilic substitution of hydrogen (ONS). It suggests that aromatization of the intermediate σ^H-adduct (Scheme 26) proceeds by action of an oxidative agent: either an external one (e.g., $KMnO_4$, CAN), or air oxygen, or one of components being present in the reaction mixture, for example, the starting nitro compound [5].

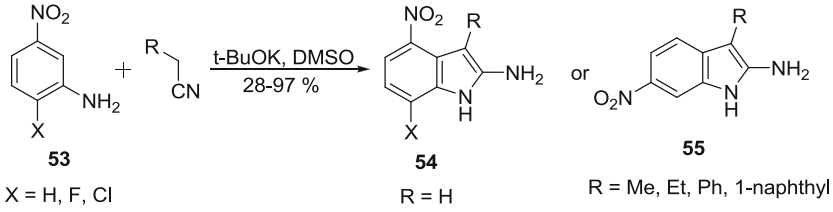
The ONS reactions usually occur at the *ortho*- and/or *para*-positions of nitroarenes relative to the nitro group depending on the structure of reagents.



Scheme 26 Oxidative nucleophilic substitution of hydrogen (general scheme)



Scheme 27 A simple and convenient method for the synthesis of indoles



Scheme 28 The ONS approach to 2-aminoindoles

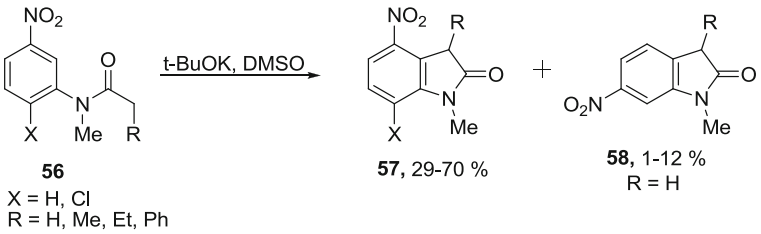
It is a common knowledge that ONS reactions allow one to introduce substituted alkyl fragments or heteroatom functional groups in nitroarenes. There are plenty of examples illustrating intramolecular ONS processes leading to the formation of heterocyclic compounds. However, in this section, we will focus only on the reactions, which give rise to the formation of nitrogen-containing heterocycles.

One of the simplest methods for indole synthesis was accomplished when *meta*-nitroanilines **51** were treated with carbonyl compounds in the presence of base (Scheme 27). The authors have suggested that the intermediate σ^H-complexes undergo oxidation by atmospheric oxygen followed by cyclization into indoles **52** [54].

It is worth noting that in addition to 4-nitroindoles **52**, the major products, the formation of 6-nitroindoles in trace quantities has been observed.

The steric factor has a significant influence on the direction of ONS in *meta*-nitroanilines **53** by action of substituted acetonitriles [55] (Scheme 28). In case of acetonitrile (R = H), the ONS process takes place at the *ortho*-position relative to the nitro and amino groups, whereas in other cases, the group X is replaced. An air oxygen is likely to act as oxidant, similarly to the abovementioned reactions.

The intramolecular ONS in *meta*-nitroanilides **56** affords oxoindole derivatives **57** [56, 57] (Scheme 29). In addition, 6-nitroindole **58** was obtained in the reaction with acetamide.

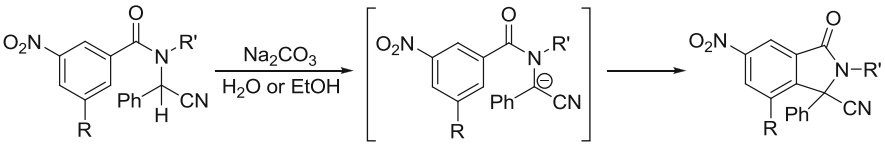


56
X = H, Cl
R = H, Me, Et, Ph

57, 29-70 %

58, 1-12 %
R = H

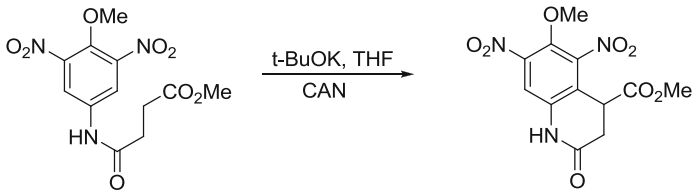
Scheme 29 Synthesis of substituted 2-oxoindoles



59
R = H, NO_2
R' = Me, Ph, Bn

60, 20 - 62 %

Scheme 30 Use of intramolecular ONS of hydrogen for the synthesis of isoindoles



61

62, 55%

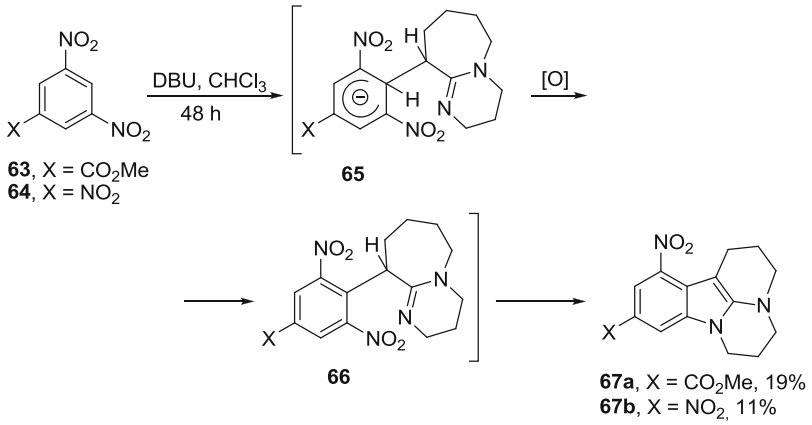
Scheme 31 Application of ONS to the synthesis of natural products

Being heated in aqueous or ethanolic Na_2CO_3, amides **59** are converted into isoindoles **60** in moderate yields. At the same time, use of an external oxidant increases yields of the products [58] (Scheme 30).

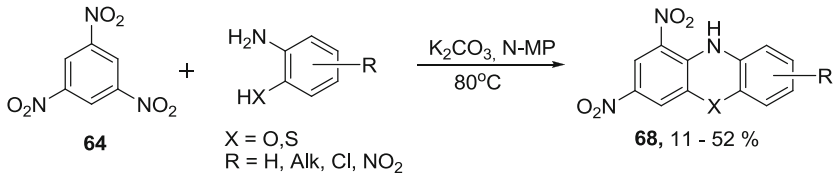
Another example, illustrating use of intramolecular ONS reactions for the synthesis of N-heterocycles, is shown in Scheme 31. In this case, the annelation of a six-membered heterocycle proceeds by action of *t*-BuOK as base and CAN as an oxidant. The cyclization product **62** seems to be intermediate for the synthesis of makaluvamine C, the naturally occurring antitumor agent [59, 60].

A sequence of ONS and nucleophilic *ipso*-substitution has been described to occur in di- and trinitrobenzene series by action of DBU [61] (Scheme 32).

The initially formed σ-complex **65** is most likely to be oxidized by the starting nitro compounds into the intermediate **66**, which in turn undergoes intramolecular substitution of the nitro group to give polycyclic compounds **67** in low yields (Scheme 32).



Scheme 32 Reaction of polynitrobenzenes with DBU



Scheme 33 S_N^{ipso}-S_N^H sequence as a pathway to phenoxazines and phenothiazines

Similarly, 1,3,5-trinitrobenzene **64** reacts with O,N- and S,N-bifunctional nucleophiles (aminophenols and aminothiophenols) [62]. As a result, 1,3-dinitrophenoxazines and 1,3-dinitrophenothiazines **68** were isolated, respectively (Scheme 33).

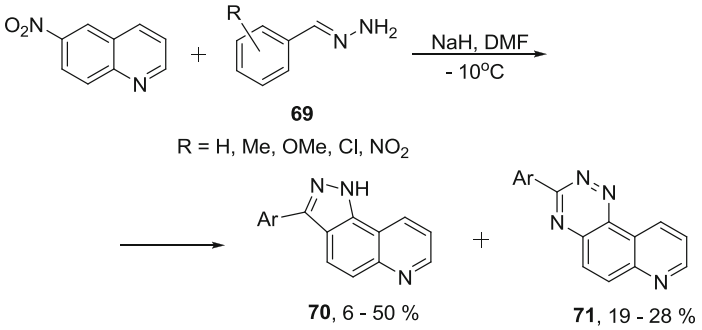
We have established that the starting nitro compound, not air oxygen, is likely to be an oxidizing agent, since these reactions proceed pretty well under inert atmosphere.

Cyclocondensation takes place on reacting 6-nitroquinoline with substituted hydrazones **69** (Scheme 34) in the presence of NaH in DMF, thus giving rise to 3-aryl-1(3)H-pyrazolo[3,4-f]quinolines **70** and/or 3-aryl[1.2.4]triazino[6,5-f] quinolines **71** [63, 64]. Yields are varied from low to moderate, while the direction of the reaction depends mainly on the structure of hydrazones: electron-donating groups in the benzene ring of hydrazones favor the triazine ring formation.

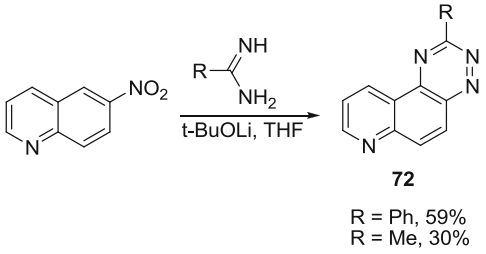
Isomeric triazinoquinolines **72** were synthesized by cyclocondensation of 6-nitroquinoline with amidines [65] (Scheme 35).

The same authors reported that the reaction of nitronaphthalenes **73** with guanidines in the presence of t-BuOLi gave amino-1,2,4-triazines **74** fused with naphthalene [65] (Scheme 36).

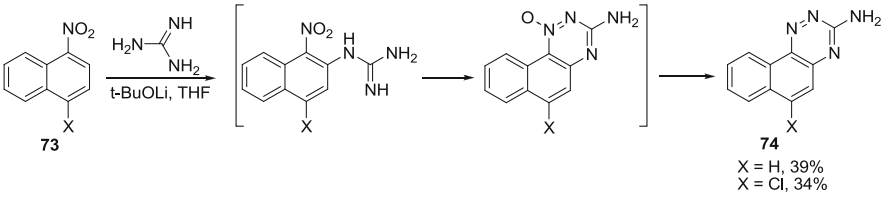
The reaction of 4-substituted 3-fluoronitrobenzenes **75** with guanidine results in the formation of a mixture of isomeric benzotriazines with a predominance of compound **76** [66] (Scheme 37). The first step of this process is likely to be ONS



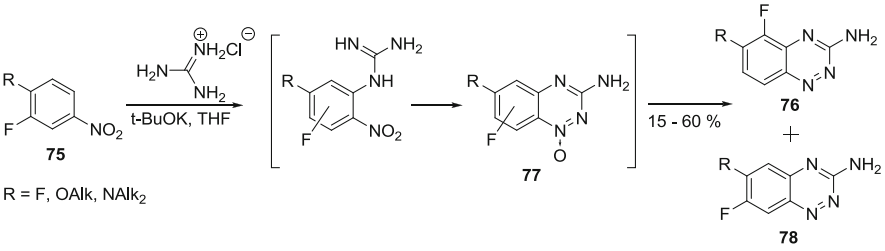
Scheme 34 Synthesis of N-heterocycles from 6-nitroquinoline



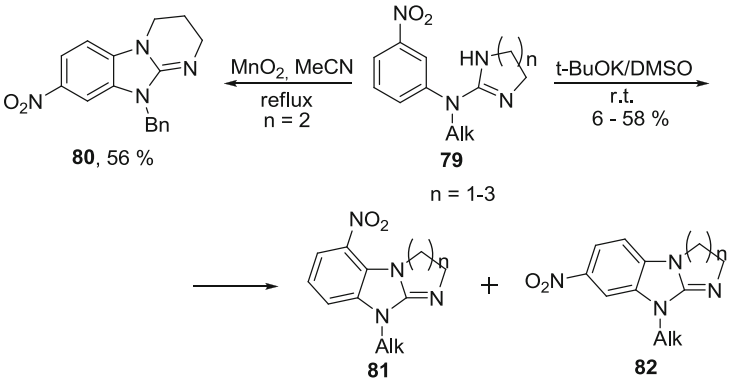
Scheme 35 Synthesis of fused triazinoquinolines from 6-nitroquinoline



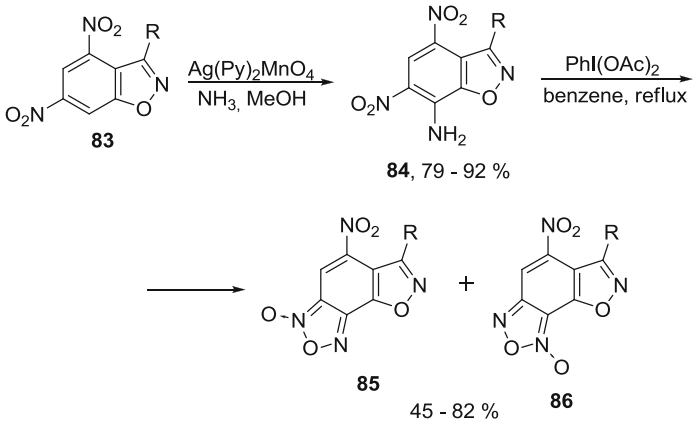
Scheme 36 ONS in nitronaphthalene series leading to naphthotriazines



Scheme 37 Synthesis of benzotriazines



Scheme 38 Synthesis of condensed benzimidazoles through the ONS of hydrogen



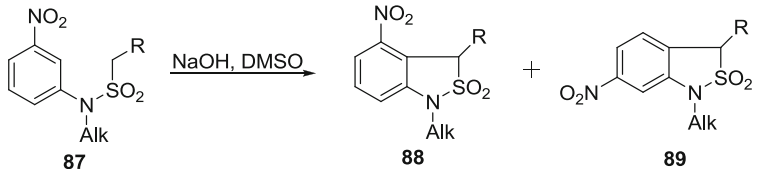
Scheme 39 Oxidative amination and cyclizations of 4,6-dinitrobenzo[*d*]isoxazoles

of hydrogen with guanidine residue by action of air oxygen followed by the intramolecular condensation on the nitro group to give the corresponding N-oxides **77**, which can further be reduced into aminobenzotriazines **76** and **78**.

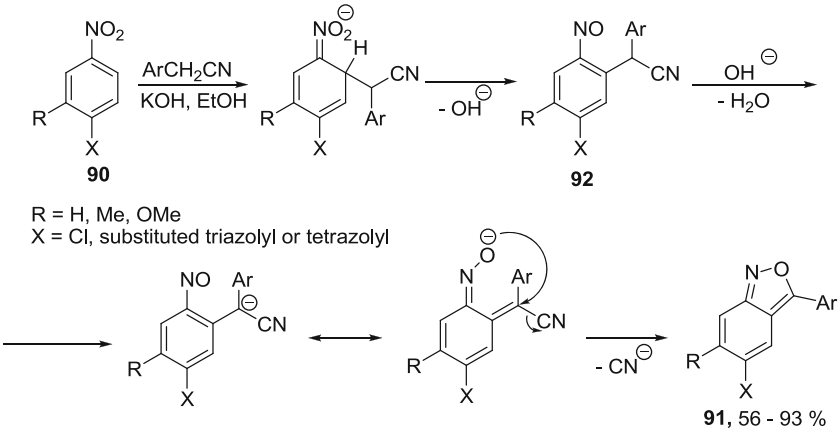
The fused benzimidazoles can also be obtained based on the intramolecular ONS reactions of cyclic guanidines **79** [67] (Scheme 38).

The direction of the ONS substitution reactions depends on the nature of an oxidant. Thus, use of MnO_2 gave compound **80** as a single product. When no external oxidant was added, a mixture of *ortho*- and *para*-substitution products **81** and **82** was obtained.

Amination of benzo[d]isoxazoles **83** proceeds regioselectively under the ONS conditions, thus leading to *ortho*-nitroamines **84** [47] (Scheme 39). The reaction was carried out in a saturated methanolic solution of NH_3, with the silver complex $Ag(Py)_2MnO_4$ being used as an oxidant. Treatment with $PhI(OAc)_2$ allowed to convert amines **84** into furoxan derivatives. According to the ^1H NMR data the reaction product in DMSO solution existed as two isomers **85** and **86** in the ratio of 5:1.



Scheme 40 Cyclization of *meta*-nitrophenyl substituted sulfonamides



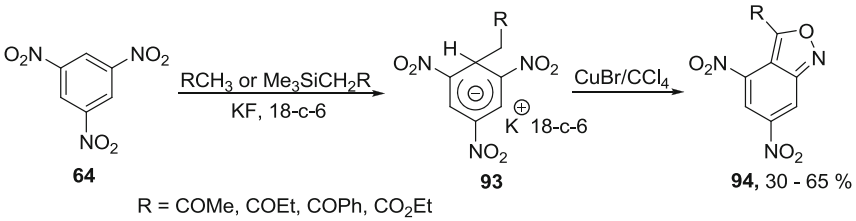
Scheme 41 Synthesis of anthranils through the intramolecular redox process

The intramolecular addition of carbanions **87** generated from N-alkylsulfonamide does occur predominantly at the *ortho*-position relative to the nitro group [24, 68, 69] (Scheme 40). The oxidation of σ^H-adducts into the target compounds **88** and **89** proceeds most likely by action of air oxygen.

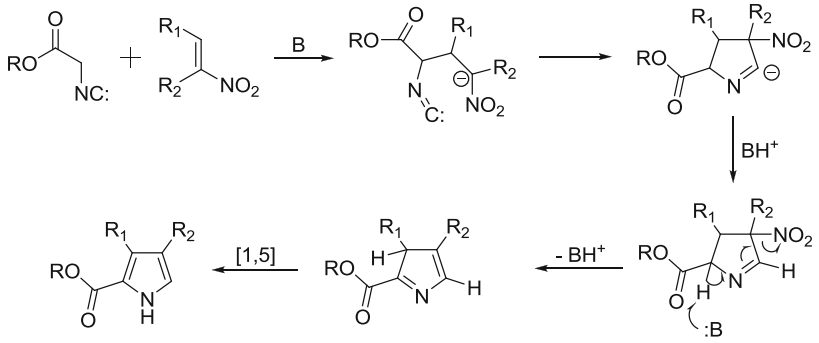
Sometimes the nucleophilic addition at carbon atom of the nitroaromatic ring may cause aromatization to go through transformation of the σ^H-adduct into a nitroso compound (i.e., via intramolecular redox process). In other words, oxidation of σ^H-adduct proceeds due to reduction of the nitro group. The resulting nitroso compounds undergo further transformations, including heterocyclizations. For example [70, 71], the reaction of *para*-chloronitrobenzenes **90** with phenyl acetonitrile in the presence of KOH affords benzo[*c*]isoxazoles **91**. The authors suggest the formation of **91** through intermediacy of the corresponding nitroso compound **92** (Scheme 41).

Oxidation of anionic σ^H-adducts of 1,3,5-trinitrobenzene (**93**) [72] by action of $CuBr/CCl_4$ provides an access to 3-substituted 4,6-dinitrobenzo[*c*]isoxazoles **94** (Scheme 42). This approach gives one more example of the formation of N-heterocycles based on the ONS process in nitroarenes.

In summary, we have discussed the very representative examples of how nitroarenes can be used as precursors for the synthesis of nitrogen heterocycles on the basis of S_N^H reactions. A number of publications dedicated to elucidation of



Scheme 42 Oxidation of TNB anionic σ-adducts



Scheme 43 The Barton–Zard reaction (general scheme)

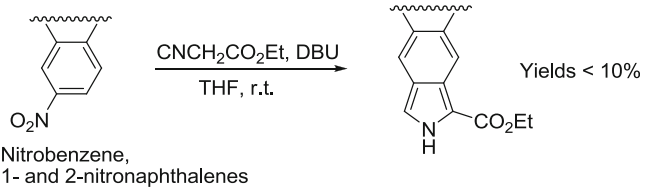
such processes are growing permanently [6, 9, 10, 73]. It undeniably indicates a considerable interest in the S_N^H methodology, which is now widely used in heterocyclic chemistry.

3 Barton–Zard Reaction

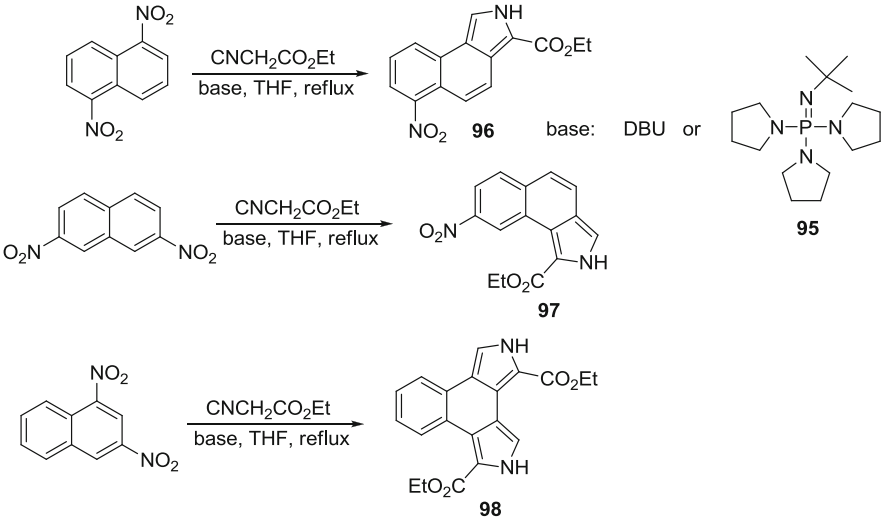
It is a common point of view that the Barton–Zard reaction is a favorable one for the pyrrole synthesis. It is based on interaction of conjugated nitroalkenes with isocyanoacetates in the presence of a base [6, 74–76] and, basically, involves three steps (Scheme 43): the Michael-type addition of isocyanide carbanion to the C=C double bond of nitroalkene, cyclization of the resulting anion to give pyrroline derivative, and elimination of the nitrite anion followed by aromatization.

Nitroarenes [77–79] and nitrohetarenes [80] have been used, instead of nitroalkenes, in similar cyclizations providing an access to fused pyrrole derivatives, isoindoles, and other polyheterocyclic systems.

The reactions of nitrobenzene and 1- and 2-nitro-substituted naphthalenes with ethyl isocyanoacetate in the presence of DBU were found to proceed very slowly [81, 82], and yields of the target isoindoles proved to be extremely low, with conversion of the starting nitro compounds not exceeding 10% (Scheme 44).



Scheme 44 Attempted synthesis of isoindoles from mononitro-substituted aromatic compounds



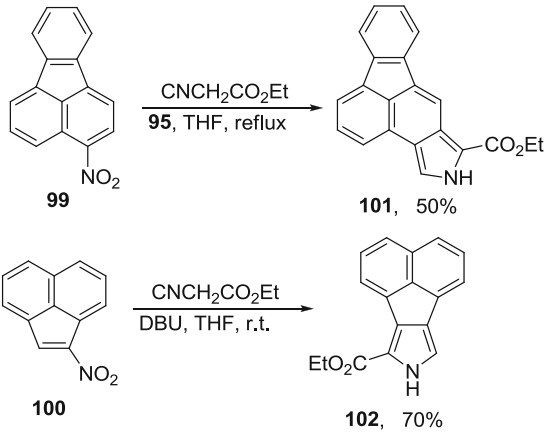
Nitro compound	Product	Yield (with DBU)	Yield (with **95**)
1,5-Dinitronaphthalene	**96**	45	78
2,7-Dinitronaphthalene	**97**	44	71
1,3-Dinitronaphthalene	**98**	25	31

Scheme 45 Synthesis of benzo-fused isoindoles from dinitronaphthalenes

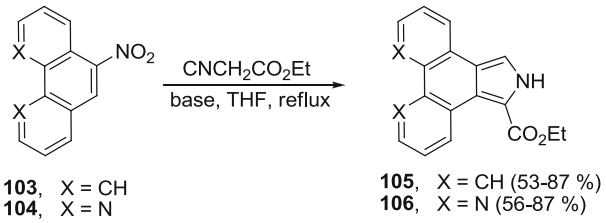
However, nitroaromatic compounds with a profound nitroalkenic character, as well as their dinitro derivatives, proved to undergo the Barton–Zard reaction much easier to give moderate-to-good yields of the target products. Indeed, 1,3-, 1,5-, and 2,7-dinitronaphthalenes gave the corresponding isoindoles in the presence of DBU in 25–45% yields [82, 83] (Scheme 45). When the phosphazene base **95** was used instead of DBU, it became possible to increase yields of isoindoles up to 31–78%. Besides, the formation of *bis*-annelation product **98** was observed in case of 1,3-dinitronaphthalene.

Polycyclic nitroaromatic compounds **99** and **100** have been found to react with alkyl isocyanoacetates into the corresponding pyrroles **101** [82] and **102** [81, 84] (Scheme 46).

Scheme 46 Annelation of the pyrrole ring to polycyclic aromatics



Scheme 47 Synthesis of dibenzo- and dipyridinoisoindoles via the Barton–Zard condensation



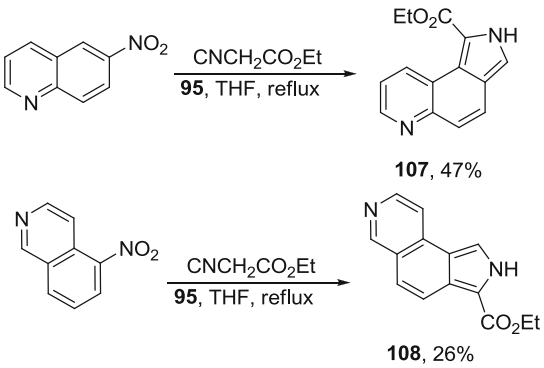
Analogously, nitrophenanthrene and phenanthroline derivatives **103** and **104** (Scheme 47) were transformed into dibenzo- and dipyridinoisoindoles, respectively [77, 81, 84, 85].

Other derivatives of the family of benzo-annelated heterocycles bearing the nitro group in the benzene ring react in a similar manner. For instance, the reaction of 6-nitroquinoline with ethyl isocyanoacetate results in the formation of isoindole **107** in 47% yield, while 5-nitroisoquinoline gave compound **108** in 26% yield [82] (Scheme 48). It should be emphasized that, in this particular case, phosphazene **95** was effective as a base, because use of DBU did not give any fused pyrroles.

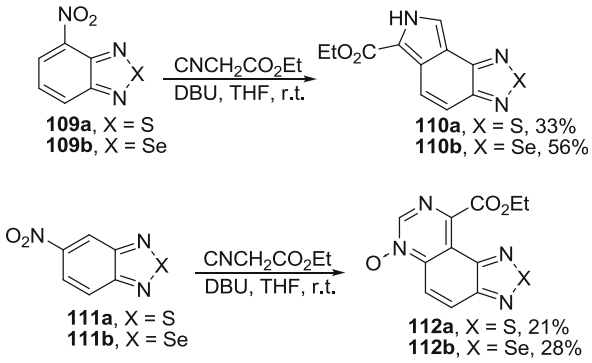
However, the Barton–Zard reaction seems to be rather sensitive to the structure of starting nitroarenes, and depending on position of the nitro group, the reaction results in the formation of various heterocycles. 4-Nitrobenzothia- and selenadiazoles have been shown to react with ethyl isocyanoacetate/DBU to give the expected isoindoles in moderate yields [78, 81, 86], while isomeric 5-nitro derivatives afford pyrimidines fused with benzoazoles under the same reaction conditions [78] (Scheme 49).

It has been found that the target isoindoles can be obtained in the presence of phosphazene **95** [87] (Scheme 50), while fused pyrimidines **112** were isolated only as traces.

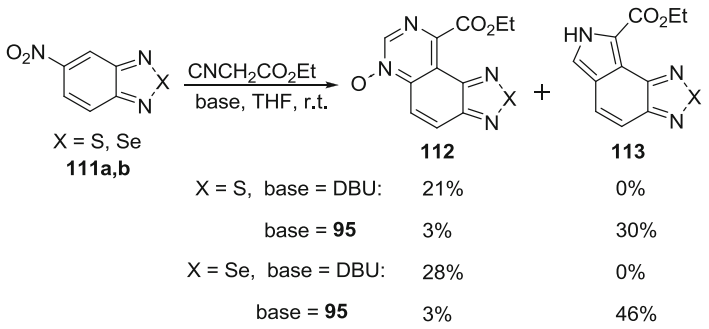
Varying base allows to obtain a wide range of functionalized isoindoles fused with the thiadiazole ring or bearing substituents in the pyrrole ring [88].



Scheme 48 Synthesis of pyridino-annelated isoindoles

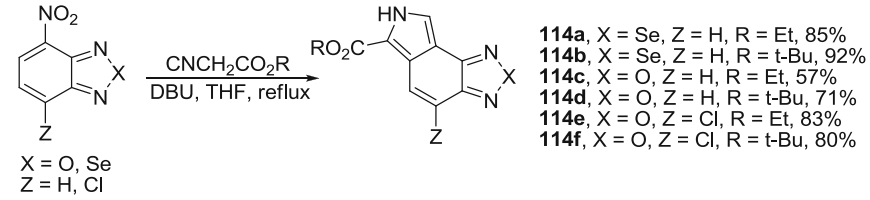


Scheme 49 The Barton–Zard reaction of 4- and 5-nitrobenzoazoles

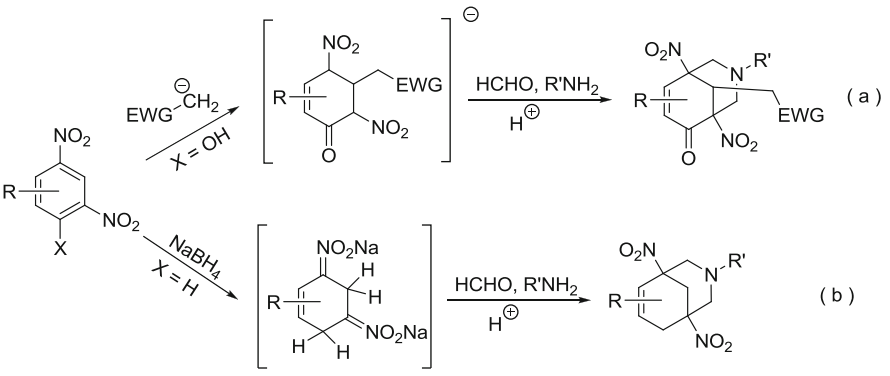


Scheme 50 The Barton–Zard reaction of 5-nitrobenzoazoles

C.M. Cillo et al. reported on the synthesis of porphyrins condensed with 2,1,3-benzoxa- and selenadiazoles [89]. Also pyrrolobenzodiazoles **114** were prepared by the Barton–Zard reaction from 4-nitrobenzofurazans or benzoselenadiazoles and isocyanoacetic esters in the presence of DBU (Scheme 51).



Scheme 51 The Barton–Zard reaction of 4-nitrobenzoazoles



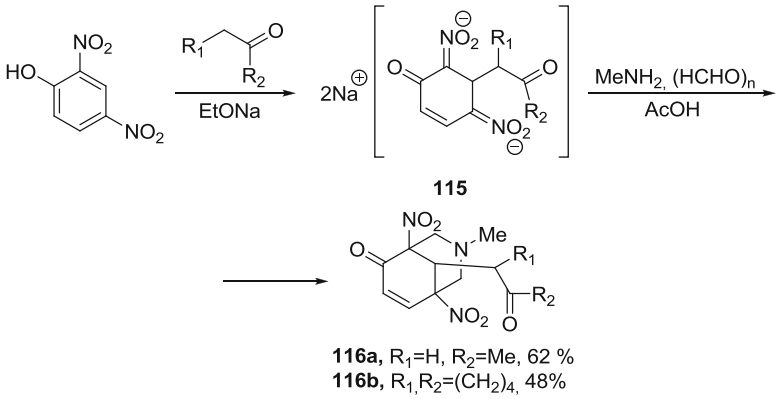
Scheme 52 Formation of anionic adducts of nitroarenes and subsequent Mannich cyclizations

The authors have shown that low yields of condensation products described in the earlier publications are mainly due to a low solubility of the starting nitro compounds in THF. It was found that yields could be considerably higher if the reactions were carried out in dilute solutions [83, 86, 89].

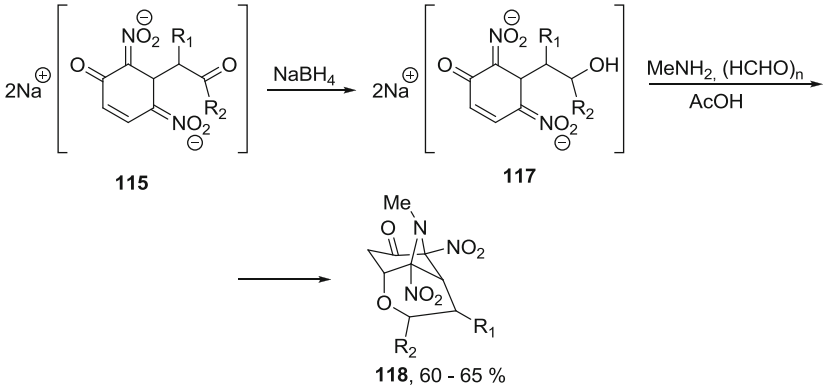
From the data considered above it is clear that the Barton–Zard condensation of nitroarenes is a convenient method for the synthesis of polycyclic compounds of the isoindole family. Formally the reaction involves the S_N^H process and further cyclization into the pyrrole ring accompanied by elimination of HNO_2.

4 Mannich Cyclization of Anionic Adducts of Nitroarenes

This section deals with the reactions in which the formation of N-heterocycles proceeds through the Mannich-type cyclocondensations of anionic σ-adducts of nitroarenes. The reactions of σ-adducts with formaldehyde and primary amines result in 1,3-annelation of the piperidine ring to the core structure of nitroarenes. Depending on nitroarene structure, there are two main routes for these reactions to take: (a) the σ-adduct is formed via the addition of C-nucleophile to a nitroarene bearing the hydroxy group and (b) cyclocondensation of hydride adducts of nitroarenes, where the hydride ion acts as a nucleophile. At least two *meta*-positioned nitro groups in aromatic ring are necessary for these reactions to proceed. Scheme 52 demonstrates both of these options.



Scheme 53 Synthesis of 1,5-dinitro-3-azabicyclo[3.3.1]non-6-enes

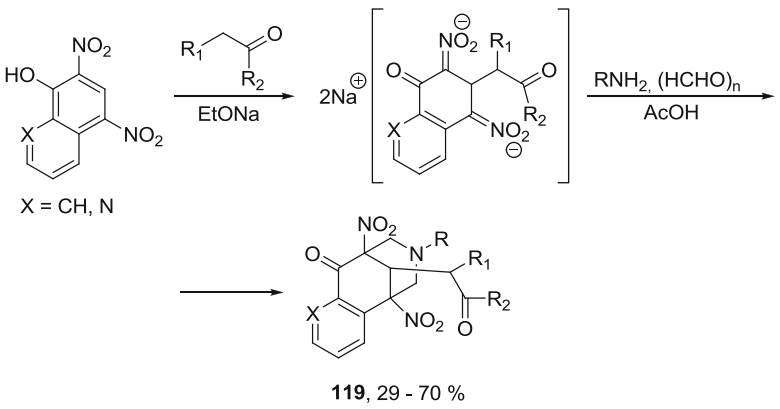


Scheme 54 Cyclization of anionic adducts of nitroarenes

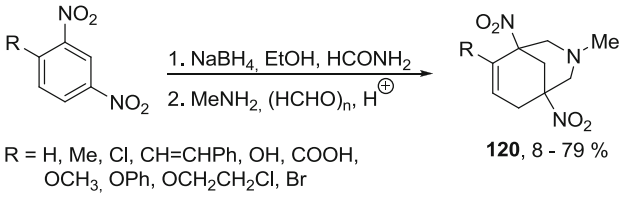
Scheme 53 illustrates the path (a). In one of the pioneer publications on such type of transformations, Severin et al. [90] described the interaction of disodium salt **115** (adduct of 2,4-dinitrophenol and acetone) with methylamine and formaldehyde in the presence of acetic acid. As a result, bicyclic derivative **116a** of 3-azabicyclo [3.3.1]nonane was isolated in 62% yield (Scheme 53). Analogous product **116b** was obtained in 48% yield, when cyclohexanone was used as C-nucleophile [90].

Another research group has applied this approach to the synthesis of polyfunctional 3-azabicyclo[3.3.1]nonanes from 2,4-dinitrophenol [91]. It has been reported that various alkyl amines and amino acids can be successfully used in these transformations.

Reduction of adducts **115** with sodium borohydride proceeds selectively on non-conjugated carbonyl group [90]. Treatment of alcohols **117** with methylamine and formaldehyde results in the formation of polycyclic compounds **118** (Scheme 54).



Scheme 55 Synthesis of benzo- and pyridine-annelated 3-azabicyclo[3.3.1]nonanes



Scheme 56 Synthesis of 1,5-dinitro-3-azabicyclo[3.3.1]non-6-enes

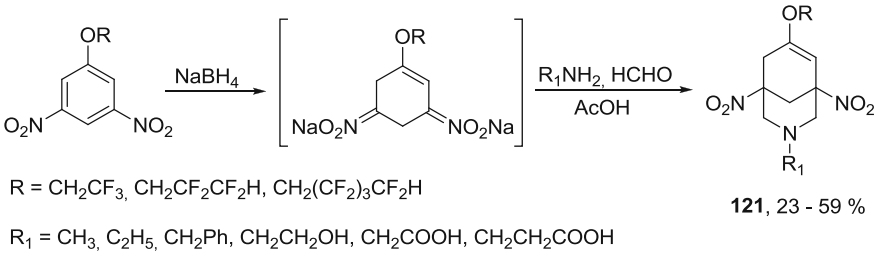
A number of condensed 3-azabicyclo[3.3.1]nonanes **119** were synthesized from 2,4-dinitronaphthol [92, 93] and 5,7-dinitro-8-hydroxyquinoline [94] (Scheme 55).

Another pathway to 3-azabicyclo[3.3.1]nonanes from nitroarenes involves the formation of hydride adducts by action of $NaBH_4$. These adducts undergo the double Mannich reaction with formaldehyde and primary amines (Scheme 52, path b). This reaction was found to take place with *meta*-dinitrobenzenes bearing a variety of functional groups. 1,3-Dinitrobenzene and its numerous derivatives were allowed to react with $NaBH_4$ followed by treatment with a mixture of methylamine, aqueous formaldehyde, and acetic acid [95–97] to give 3-azabicyclo[3.3.1]nonanes **120** (Scheme 56).

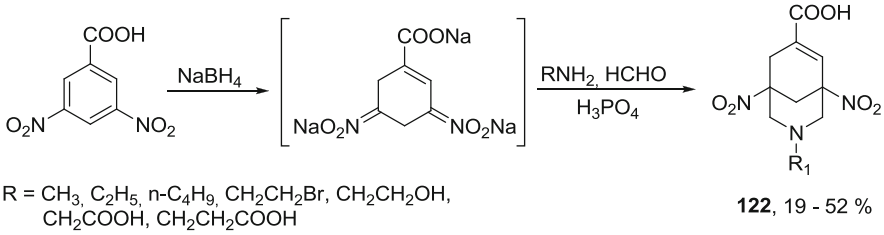
A number of 7-polyfluoroalkoxy 1,5-dinitro-3-azabicyclo[3.3.1]non-6-enes **121** were synthesized by means of reduction of polyfluoroalkyl ethers of 3,5-dinitrophenol with sodium borohydride followed by the Mannich reaction with formaldehyde and alkyl amines [98] (Scheme 57).

3,5-Dinitrobenzoic acid has been shown to undergo the Mannich cyclization similarly to give the corresponding azabicyclo[3.3.1]non-6-enes **122** in moderate yields [99] (Scheme 58).

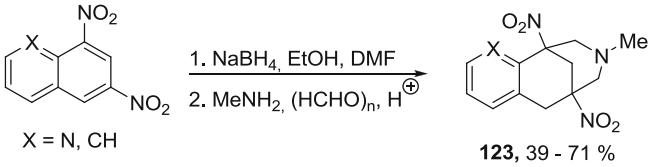
meta-Dinitronaphthalene and its quinoline analogue have been shown to react smoothly with $NaBH_4$, followed by cyclization into 3-azabicyclo[3.3.1]nonanes **123** fused with the benzene or pyridine ring, respectively [100] (Scheme 59).



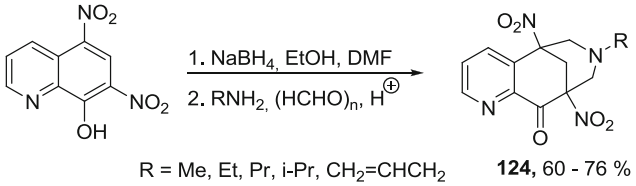
Scheme 57 Synthesis of polyfluoroalkoxy 1,5-dinitro-3-azabicyclo[3.3.1]non-6-enes



Scheme 58 Cyclization of the hydride adducts



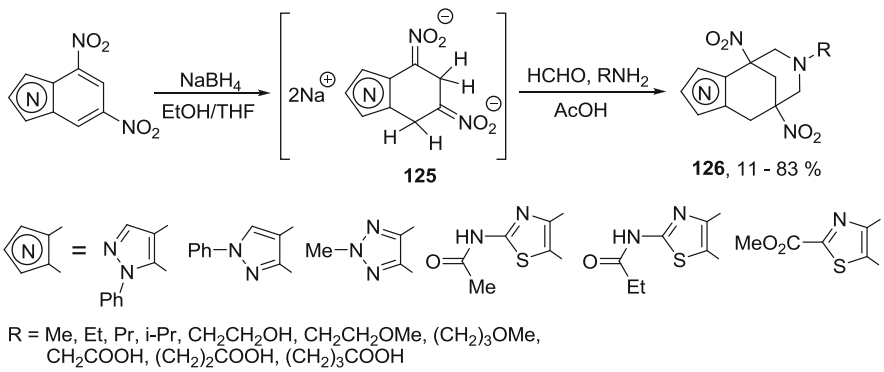
Scheme 59 Bicyclic nitroarenes as precursors of fused 3-azabicyclo[3.3.1]nonanes



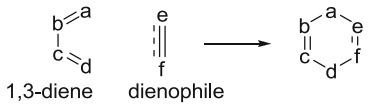
Scheme 60 Synthesis of 3-azabicyclo[3.3.1]nonanes fused with the pyridine ring

In a similar cyclization of 8-hydroxy-5,7-dinitroquinoline the corresponding ketones **124**, in which the 3-azabicyclo[3.3.1]nonane skeleton is fused with the pyridine ring, have been isolated [101] (Scheme 60).

The data on the synthesis of azabicyclo[3.3.1]nonanes fused with azoles have recently been published [102–104]. The first step of the reaction is the formation of hydride adducts **125** by action of $NaBH_4$ (Scheme 61). These adducts undergo the Mannich condensation with formaldehyde and alkyl amines to give 3-R-1,5-dinitroazabicyclo[3.3.1]nonanes **126**, fused with azole fragments across the C(7)–C(8) bond.



Scheme 61 Synthesis of 3-azabicyclo[3.3.1]nonanes fused with azoles



Scheme 62 [4+2] Cycloaddition (the Diels–Alder reaction)

In conclusion it is worth noting that 1,3-dinitrobenzenes, bearing functional groups, as well as their structural analogues with the fused benzene ring or N-heterocyclic fragments can be regarded as appropriate substrates for preparation of a variety of 3-azabicyclo[3.3.1]nonanes via the Mannich condensation of intermediate σ^H-adducts, derived from the addition of carbanions, or the hydride ion at unsubstituted C-2 of 1,3-dinitroarenes.

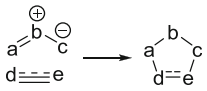
5 Pericyclic Reactions of Nitroarenes

Pericyclic cycloaddition reactions have attracted a considerable interest of chemists due to some distinct advantages. First of all, a new ring is formed from two reacting molecules without elimination of any group or atom. Secondly, the reactions are accompanied by overall decrease in bond multiplicity. The most significant pericyclic cycloaddition reactions are [4+2]-cycloaddition (Diels–Alder reaction) and [3+2]-cycloaddition (1,3-dipolar cycloaddition) [105–107].

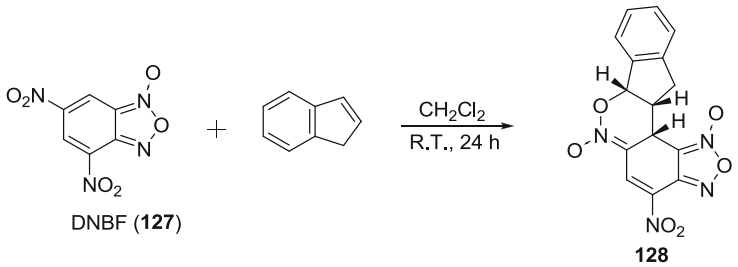
The [4+2]-cycloaddition reactions lead to the formation of six-membered rings through interaction of conjugated 1,3-dienes (4π system) with alkenes and acetylenes (dienophiles, 2π system) [108] (Scheme 62).

1,3-Dienes and dienophiles are usually to undergo [4+2] cycloaddition reactions in those cases when these compounds contain activating groups.

Carbocyclic compounds are formed if all atoms a-f are carbons. However, a variety of heterodienes, such as C=C–C=N, C=C–C=O, and N=C–C=N, as well



Scheme 63 [3+2] Cycloaddition reaction



Scheme 64 Reaction of DNBF with indene

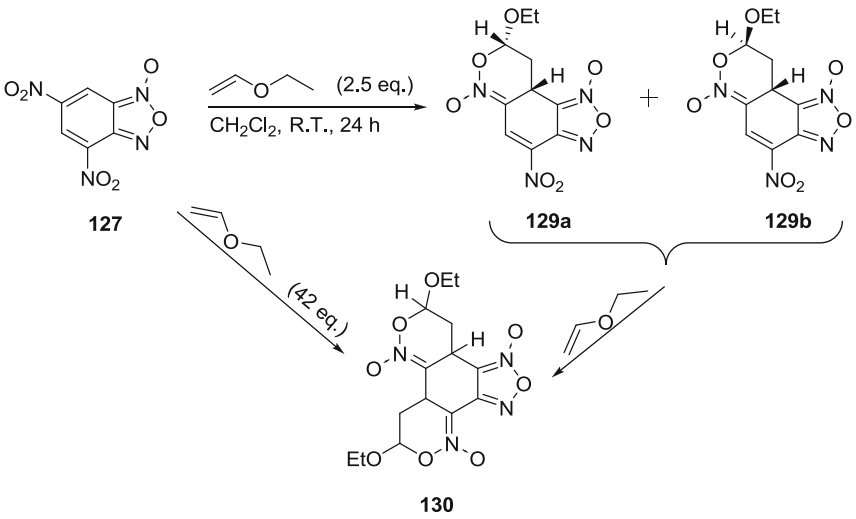
as heterodienophiles, such as –C=N, –C=O, –C=S, –N=N–, –S=O, and –N=O, can also undergo [4+2]-cycloaddition reactions to give six-membered heterocycles. [4+2] Cycloaddition appears to be one of the most widely applied reactions in organic chemistry [106, 108–110]. It is used for the synthesis of various polycyclic compounds, including enantioselective [4+2] cycloadditions, which proved to be an effective synthetic tool to obtain natural compounds and their analogues [111, 112].

[3+2]-Cycloaddition (1,3-dipolar cycloaddition) involves the addition of 1,3-dipolar molecules to multiple bonds of various dipolarophiles leading to five-membered heterocycles [113, 114] (Scheme 63).

5.1 [4+2]-Cycloaddition Reactions

The publication of Terrier et al. [115] appears to be the first major contribution to understanding of such transformations. These researchers have observed that mixing of equimolar amounts of 4,6-dinitrobenzofuroxan (DNBF, **127**) and indene in DMSO, CH_2Cl_2, or methanol results in the formation of the product with unusual spectral characteristics, which are significantly different from those of the previously isolated σ-complexes of DNBF. Comparing these data with the results published earlier, the authors concluded that the compound obtained proved to be dihydro-1,2-oxazine N-oxide **128** (Scheme 64). A plausible mechanism for the formation of **128** was suggested to be either a two-step process through the σ-complex or a concerted reaction proceeding through a cyclic transition state, i.e., [4+2]-cycloaddition with an inverse electron demand (IED).

The same group of authors has reported on the formation of similar DNBF cycloadducts with other dienophiles, in particular, with ethyl vinyl ether [116]. When the reaction is carried out in the presence of 2.5 equivalents of



Scheme 65 DNBF as heterodiene in the Diels–Alder reaction

dienophile, it results in the formation of diastereomeric dihydro-1,2-oxazine N-oxides **129a** and **129b**, in the ratio 4:1(Scheme 65).

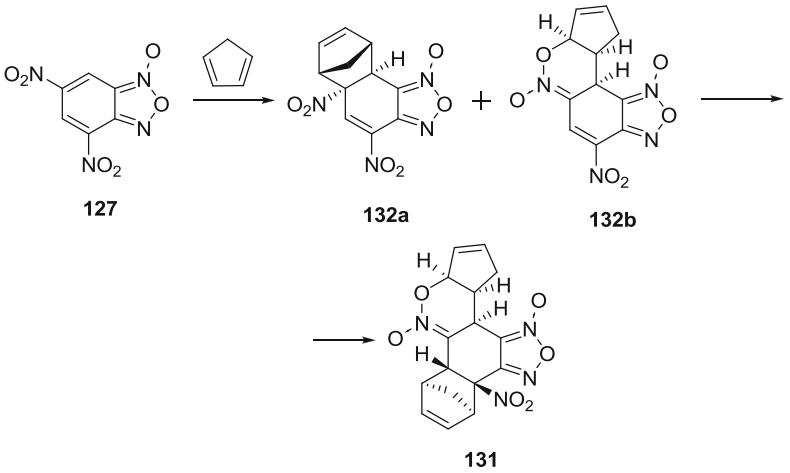
When ethyl vinyl ether was used as solvent, a mixture of several diastereomeric *bis*-adducts **130** was obtained [116]. Stereochemical features for the major products have been studied, and the reaction mechanism proved to be in agreement with an inverse electron demand cyclization.

The dual reactivity of DNBF in [4+2]-cycloaddition reactions is illustrated nicely by the reaction of benzofuroxan with cyclopentadiene [117]. The addition of an excess of the diene to a solution of **127** in chloroform at 0°C leads only to one diastereomer **131**, which has been isolated as a racemic mixture (Scheme 66).

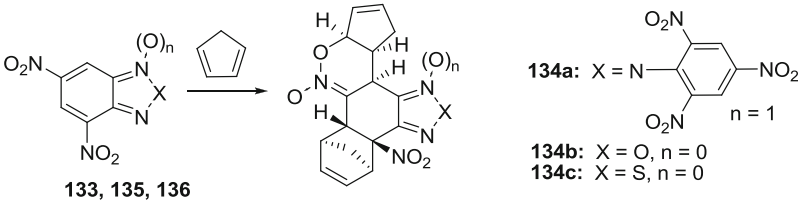
Use of ^{1}H NMR spectroscopy revealed that, at a low reaction temperature (−30°C), the adducts **132a**,**b** are initially formed, which then react subsequently upon a gradual increase of temperature into polycyclic compound **131** (Scheme 66). It is clear that at the initial step there are two competing reactions, which are in accord with NED and IED. This is the IED reaction, which leads to annelation of the oxazine ring.

Also, a number of other highly electrophilic nitroarenes (superelectrophiles, see below) were used as heterodienes in the Diels–Alder reaction. When a structural analogue of DNBF, 4,6-dinitro-2-picrylbenzotriazole-1-oxide (**133**), was treated with an excess of cyclopentadiene, the [4+2]-cycloadduct **134a** with the fused oxazine ring was obtained in 92% yield (Scheme 67) [118].

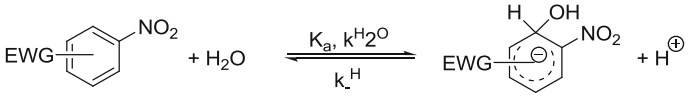
4,6-Dinitrobenzofurazan (**135**) and 4,6-dinitrobenzothiadiazole (**136**) behave similarly [119] (Scheme 67) and are capable of reacting with cyclopentadiene into *bis*-adducts **134b**,**c** in 68% and 32% yields, respectively. It is worth noting that 4,6-dinitrobenzoselenadiazole (X = Se, n = 0) did not give any stable adduct. It was later shown that this Diels–Alder reaction takes place only in the series of



Scheme 66 Cycloadducts derived from the reaction of DNBF with cyclopentadiene



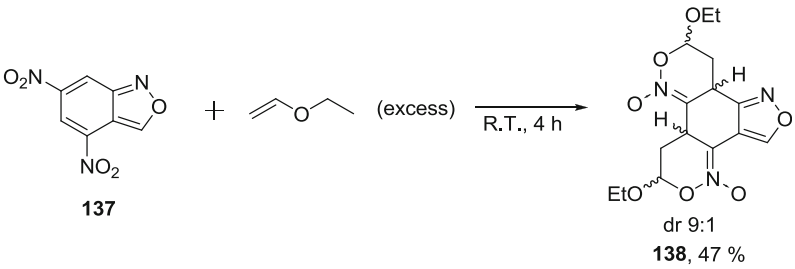
Scheme 67 4,6-Dinitrobenzoazoles as dienophiles and heterodienes



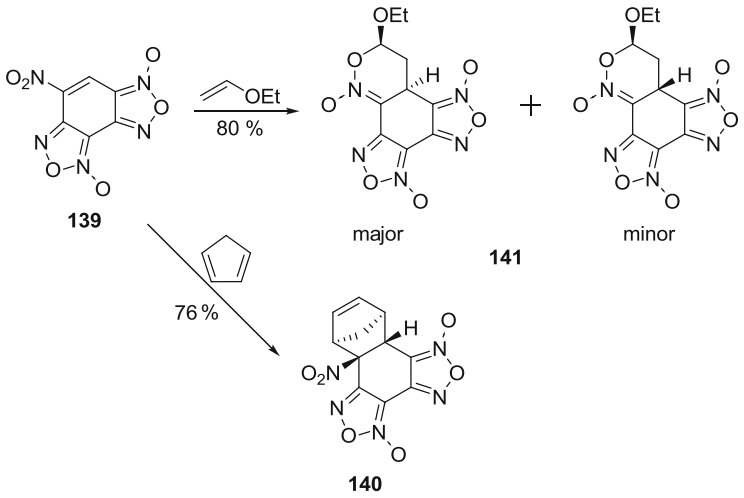
Scheme 68 Equilibrium for the σ^H-adducts formation

those nitroarenes, which were referred by F. Terrier as superelectrophiles. A characteristic feature of the latter is the ability to form anionic σ^H-adducts with water (or MeOH) without any base added [120] (Scheme 68). The equilibrium of this process is determined by $pK_a^{H_2O}$, and superelectrophiles have $pK_a^{H_2O} \leq 7.5–8$.

Another example of nitroarenes capable of undergoing [4+2]-cycloaddition with IED is 4,6-dinitrobenzo[*c*]isoxazole (**137**) [121], which can be considered as a structural analogue of 4,6-dinitrobenzofurazan (Scheme 69). Although the CH fragment replaces only one of the nitrogen atoms in the structure of benzofurazan **135**, anthranil **137** possesses the reactivity sufficient for annelation of two oxazine fragments to the benzene ring in the reaction of **137** with an excess of ethyl vinyl ether.



Scheme 69 Reaction of 4,6-dinitrobenzo[*c*]isoxazole with ethyl vinyl ether

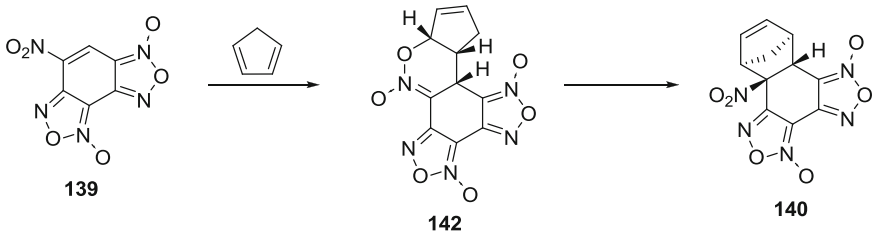


Scheme 70 NBDF as dienophile and heterodiene

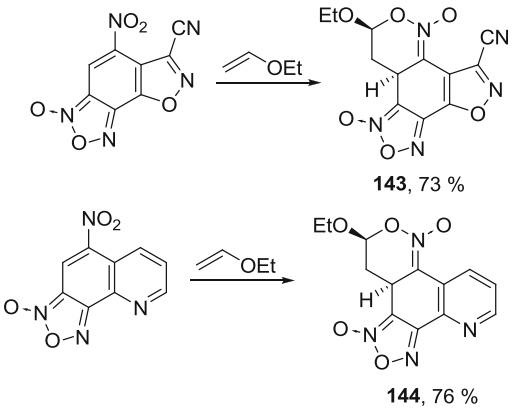
Kurbatov et al. [122] studied properties of 4-nitrobenzodifuroxan **139** (NBDF) and found that, in spite of the formal aromatic structure, the C=C–NO_2 fragment has pronounced nitroalkene character. NBDF was found to undergo cycloaddition with dienes (in accord with NED), and, as a heterodiene, it is capable of reacting with ethyl vinyl ether (in accord with IED) to give polycondensed heterocycles **140** and **141**, respectively (Scheme 70).

However, it has been established on the basis of both experimental and calculated data [123] that the reaction of **139** with cyclopentadiene proceeds through the formation of IED intermediate **142** (Scheme 71), which then rearranges into the thermodynamically more stable NED product **140**.

Superelectrophilic properties of nitroarenes are retained when one of the furoxan rings in NBDF is replaced with electron-deficient isoxazole [124] or pyridine fragments [125]. As in case of NBDF, the reactions of these fused nitroarenes with ethyl vinyl ether were found to lead to the corresponding benzoxazine N-oxides **143** and **144** condensed with heterocyclic rings (Scheme 72).



Scheme 71 The formation of NBDF-cyclopentadiene adducts



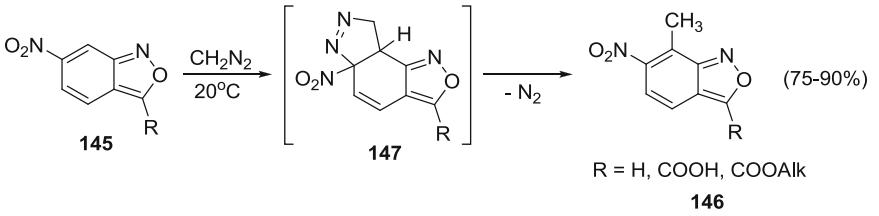
Scheme 72 Synthesis of cyclic nitronates via the Diels–Alder reaction of nitroarenes

It has to be concluded that superelectrophilic nitroarenes possess a dual reactivity in the Diels–Alder reactions, thus giving rise to the formation of either carbocyclic (NED) or heterocyclic (oxazine, IED) rings. The ability of highly electrophilic nitroarenes, as heterodienes, to undergo the Diels–Alder reaction with nucleophilic dienophiles provides a general method for annelation of one or two oxazine rings to an aromatic system. This possibility can be explained by a low aromatic character of the benzene ring activated by the nitro group and annelated heterocyclic fragments in this family of fused heteroaromatics.

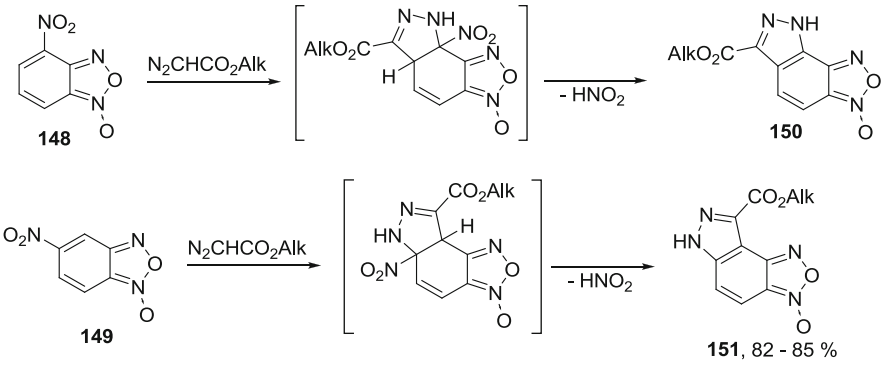
5.2 [3+2]-Cycloaddition Reactions

Nitroalkenes are known to react readily with various 1,3-dipoles to give a broad range of five-membered heterocycles [126]. Nitroarenes also contain the C=C–NO_2 fragment and, therefore, one might expect these compounds to be able to add some dipoles, at least the nucleophilic ones.

However, the data on 1,3-dipolar cycloaddition reactions of nitroarenes, acting as dipolarophiles, are scarcely available in the literature. There have been only a few



Scheme 73 1,3-Dipolar cycloaddition of diazomethane to 6-nitroanthranils



Scheme 74 Nitrobenzofuroxans in [3+2]-cycloadditions with diazoesters

examples describing the addition of aliphatic diazo compounds to the benzene ring of nitrobenzoazoles. For example, the reaction of 3-substituted 6-nitrobenzo-[*c*] isoxazoles **145** with excess of diazomethane (Scheme 73) affords 7-methyl-6-nitro compound **146** [127].

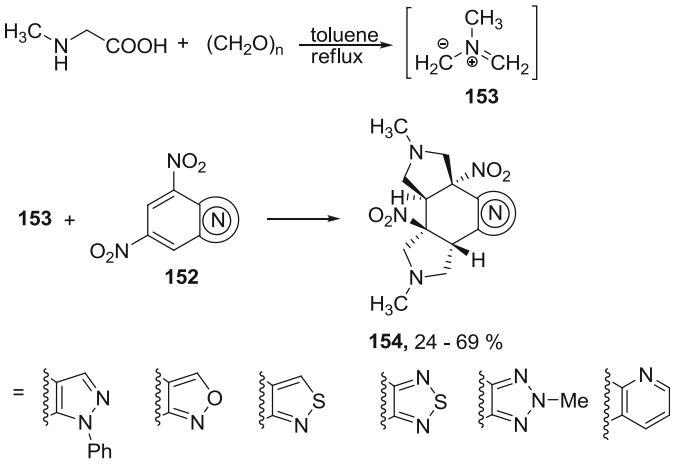
Although the intermediate [3+2] cycloadducts **147** have neither been registered nor isolated, Chandra Boruah et al. [127] claim that these intermediates can be detected chromatographically at a low temperature.

In the reactions of 4- and 5-nitrobenzofuroxans **148** and **149** with alkyl diazoacetates, the initially formed cycloadducts undergo aromatization with the loss of nitrous acid (Scheme 74) to give pyrazolobenzofuroxans **150** and **151** in good yields [128].

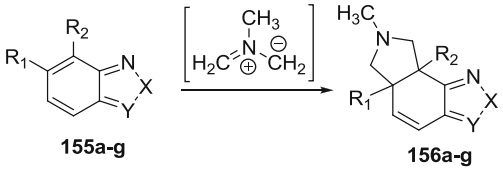
During the last decade we have been carrying out a systematic study of the reactions of nitroarenes with N-alkyl azomethine ylides. A fundamentally new approach has been advanced for the synthesis of polycyclic heterosystems bearing important pharmacophoric fragments, such as pyrrolidines, pyrrolines, and pyrroles.

The first example of the cycloaddition of azomethine ylides on an aromatic C=C double bond activated by the nitro group is the reaction of highly electron-deficient nitroaromatics, such as 4,6-dinitrobenzazoles or 6,8-dinitroquinoline **152**, with unstabilized N-methyl azomethine ylide (**153**) [129, 130] (Scheme 75).

In all cases, cycloadditions were observed across both C=C–NO_2 fragments to give polycyclic systems **154** containing two pyrrolidine rings. The reactions proved



Scheme 75 Double 1,3-dipolar cycloaddition of N-methyl azomethine ylide to dinitrobenzo heterocyclic compounds

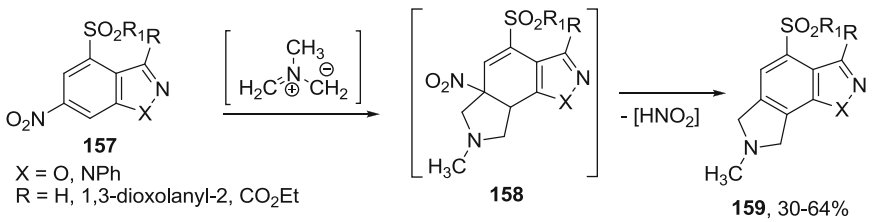


Compound	X	Y	R_1	R_2	Product	Yield (%)
155a	O	N	H	NO_2	**156a**	75
155b	S	N	H	NO_2	**156b**	42
155c	Se	N	H	NO_2	**156c**	46
155d	O	CH	NO_2	H	**156d**	40
155e	O	N	NO_2	H	**156e**	98
155f	S	N	NO_2	H	**156f**	64
155g	Se	N	NO_2	H	**156g**	47

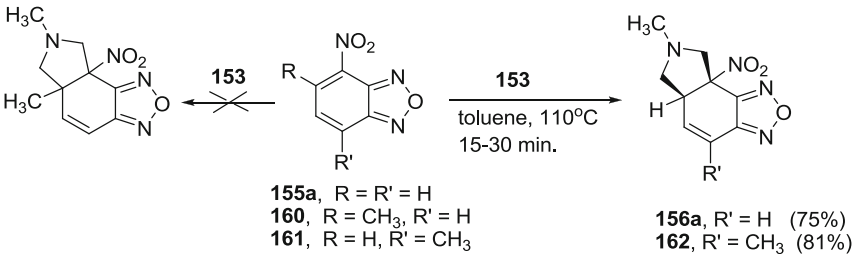
Scheme 76 Synthesis of tetrahydroisoindoles fused with azoles

to proceed in a stereoselective manner: the first and the second cycloadditions took place from different sides of the benzene ring plane. Such a behavior of dinitrobenzazoles is a characteristic feature of [4+2]-cycloaddition reactions (see, e.g., Scheme 69) and may be attributed to a diminished aromaticity and, as a consequence, increased reactivity of these aromatic systems due to the presence of two nitro groups and fused heterocycles.

It has been found [131] that mononitrobenzazoles **155** (4- and 5-nitrobenzofurazans, -thiadiazoles, -selenadiazoles, and -[*c*]isoxazoles) are able to form cycloadducts **156** with N-methyl azomethine ylide **153** (Scheme 76). This dipole adds only at the C=C bond activated by the nitro group, thus giving tetrahydroisoindoles condensed with azoles.



Scheme 77 Synthesis of isoindolines fused with azoles



Scheme 78 Synthesis of tetrahydroisoindoles fused with furazan

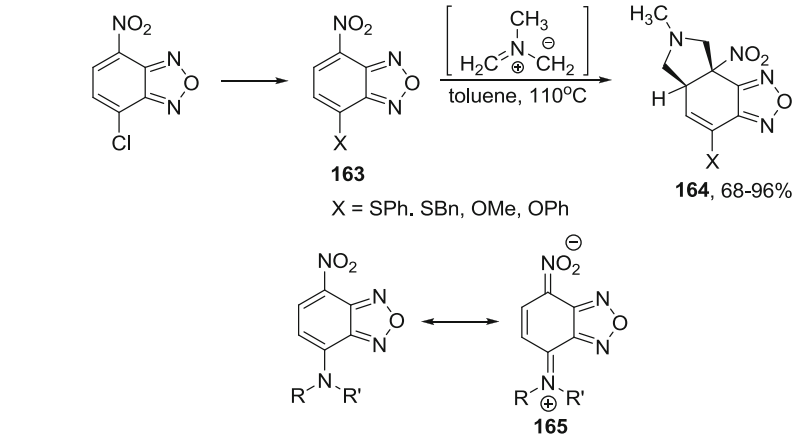
Sulfonyl derivatives **157** containing one nitro group behave analogously (Scheme 77). However, the intermediate cycloadducts **158** undergo aromatization under the reaction conditions, with the loss of nitrous acid.

It is worth noting that steric factors have a considerable effect on feasibility of 1,3-dipolar cycloaddition in the series of nitrobenzazoles. It has been shown, for instance, that 5-methyl-4-nitrobenzofurazan **160**, in contrast to 4-nitrobenzofurazan **155a**, lacking a substituent at position 5, did not form a cycloaddition product (Scheme 78) [132].

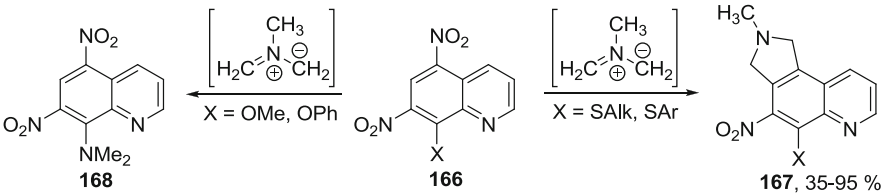
At the same time, isomeric 7-methyl-4-nitrobenzofurazan **161** proved to react with N-methyl azomethine ylide **153** in a similar to benzofurazan **155a** manner to give tetrahydroisoindole **162** in a high yield (Scheme 78).

We have also studied the [3+2]-cycloaddition of N-methyl azomethine ylide **153** to 4-X-7-nitrobenzofurazans **163** (Scheme 79) [132]. It has been established that the nature of substituent X has a significant effect on feasibility of the reaction. In case X=SR and OR, the reaction proceeds normally to give cycloadducts **164** in high yields, but when dialkylamino or arylamino group is present at the *para*-position relative to the nitro group, no cycloadduct formation is observed. This failure is likely due to a large contribution of the betaine **165** to the structure of 7-amino compounds (Scheme 79).

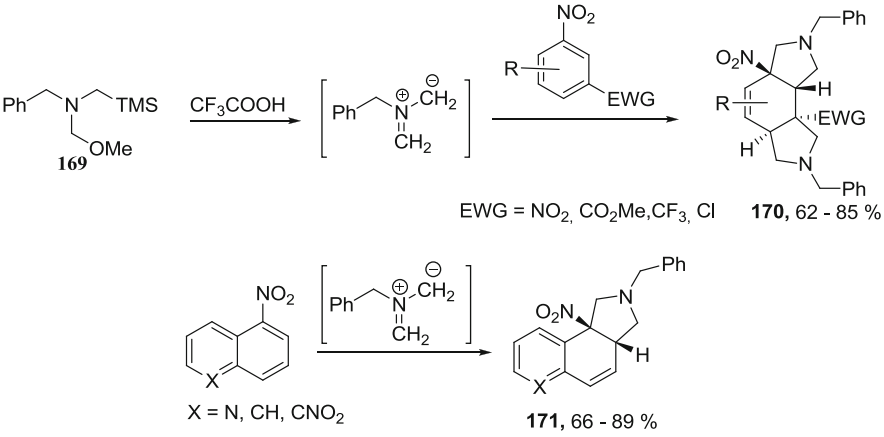
8-X-5,7-Dinitroquinolines **166** are also able to react with dipole **153** (Scheme 80). However, in this particular case, the reaction is governed by the nature of substituent X in position 8 [133]. 8-SR-Derivatives undergo the addition of this dipole exclusively across the C(5)–C(6) bond to give pyrrolines **167**. On the other hand, in case of 8-OR-derivatives, the displacement of OR- with NMe_2-group was found to be the main process.



Scheme 79 Reaction of 4-X-7-nitrobenzofurazans with N-methyl azomethine ylide

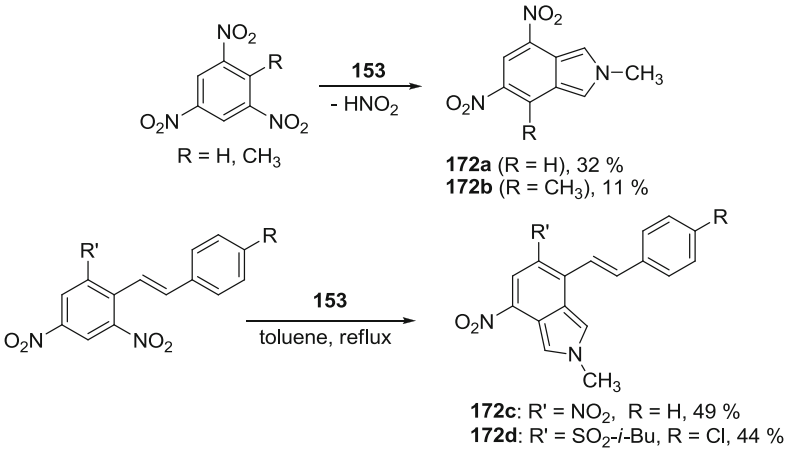


Scheme 80 Synthesis of isoindolines fused with the pyridine ring



Scheme 81 [3+2]-Cycloaddition of N-benzyl azomethine ylide with nitroarenes

Lee et al. reported on the reaction of mono- and dinitro-substituted benzenes, naphthalenes, and some other benzo-annelated heterocycles with unstabilized N-benzyl azomethine ylide, which was generated in situ from hemiaminal **169** by action of catalytic amounts of trifluoroacetic acid (Scheme 81) [134].



Scheme 82 Synthesis of functionalized isoindoles

As a result, cycloadducts containing one or two pyrrolidine rings condensed with the benzene ring were obtained depending on the molar ratio of reagents and the structure of dipolarophile. The reactions were shown to require the presence of the nitro group and another electron-withdrawing substituent in the benzene ring (mononitrobenzene does not react with azomethine ylide under these reaction conditions). However, the presence of one nitro group was sufficient in the series of naphthalenes [134].

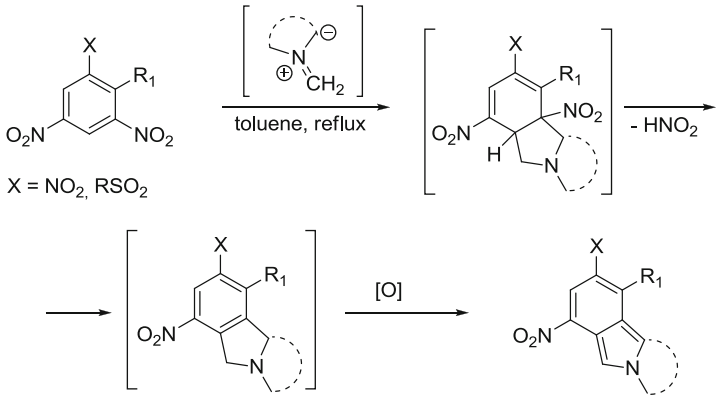
In continuation of our systematic studies, we have investigated the reactions of substituted di- and trinitrobenzenes with a series of N-alkyl azomethine ylides [135]. It has been found that 1,3-di- and 1,3,5-trinitrobenzenes react with N-methyl azomethine ylide (**153**) to give isoindoles **172** in moderate yields (Scheme 82).

It is of interest to note that, in contrast to nitrobenzazoles, after the formation of [3+2]-cycloadducts of polynitrobenzenes with this dipole, a rapid loss of HNO_2 and subsequent oxidation have been observed (Scheme 83) [135].

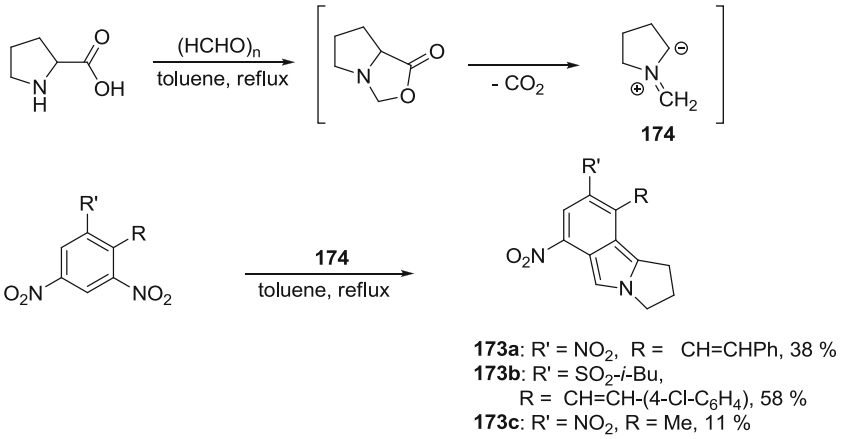
Although these reactions were carried out in the presence of air oxygen, nitroaromatic substrates were likely to be oxidizing agents, since yields proved to be the same in inert atmosphere. Furthermore, it should be noted that, in case of monocyclic di- and trinitrobenzenes, the dipole adds only across the C=C bond activated by the nitro group, specifically, at positions 2 and 3 relative to substituent R_1 (Scheme 83).

Use of cyclic amino acids instead of sarcosine to generate the corresponding dipole as well as the subsequent [3+2]-cycloaddition allowed to obtain condensed isoindoles [135]. Thus, tricyclic derivatives **173** were obtained in the case of proline (Scheme 84).

When thiazolidine-4-carboxylic acid was used under these conditions, the corresponding isoindolines **176** could not be fully oxidized to isoindoles **177** (Scheme 85).

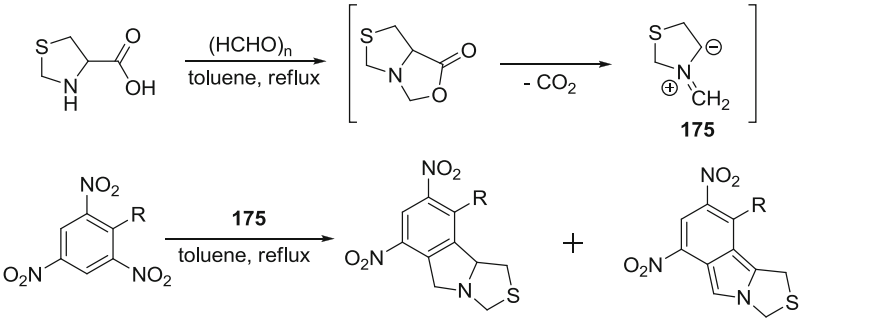


Scheme 83 Cycloaddition of N-alkyl azomethine ylides with polynitrobenzenes



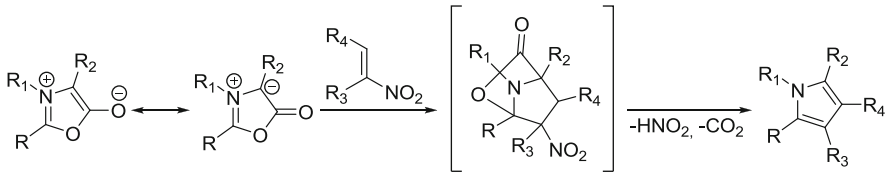
173a: R' = NO_2, R = CH=CHPh, 38 %
173b: R' = SO_2-*i*-Bu,
R = CH=CH-(4-Cl-C_6H_4), 58 %
173c: R' = NO_2, R = Me, 11 %

Scheme 84 [3+2]-Cycloaddition of the dipole derived from proline

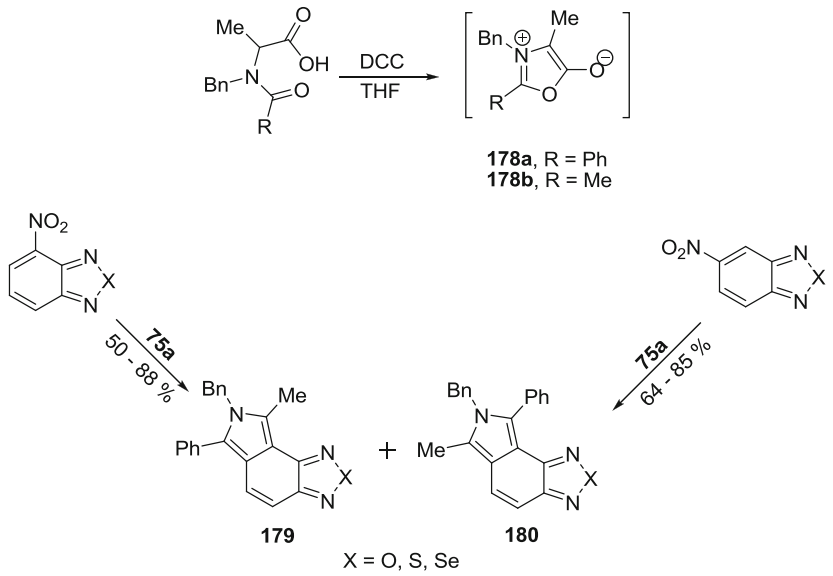


176a, R = CH_3, 34 %
176b, R = CH=CHC_6H_5, 36 % **177b,** R = CH=CHC_6H_5, 35 %

Scheme 85 [3+2]-Cycloaddition of the dipole derived from thiazolidine4-carboxylic acid



Scheme 86 1,3-Dipolar cycloaddition of münchnones to conjugated nitroalkenes

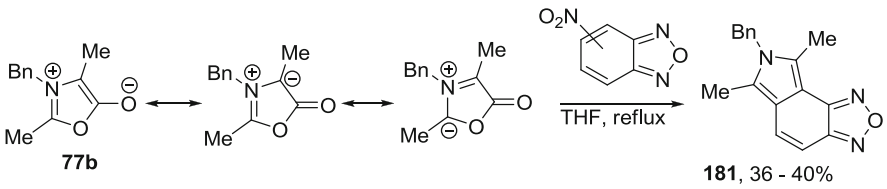


Scheme 87 1,3-Dipolar cycloaddition of münchnones to nitrobenzoazoles

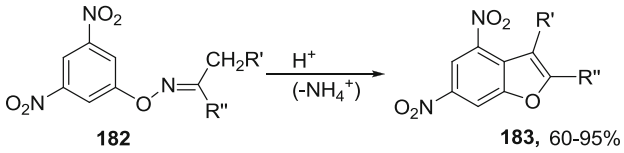
One more example of 1,3-dipolar cycloaddition with nitroarenes is the reaction of nitrobenzazoles with mesoionic 1,3-oxazolium-5-olates (münchnones) [136]. Münchnones are known to react as 1,3-dipoles with conjugated nitroalkenes [137] and some nitroheterocyclic compounds [138]. The münchnone molecule contains a cyclic azomethine ylide fragment. Thus, the reaction of this compound with nitroalkenes leads to bicyclic intermediates, which then undergo elimination of HNO_2 and CO_2 to give pyrroles (Scheme 86).

The reactions of asymmetrical münchnone **178a** with nitro derivatives of benzofurazan, benzothiadiazole, and benzoselenadiazole gave a mixture of isomeric isoindoles **179** and **180**, condensed with the corresponding azoles [136] (Scheme 87).

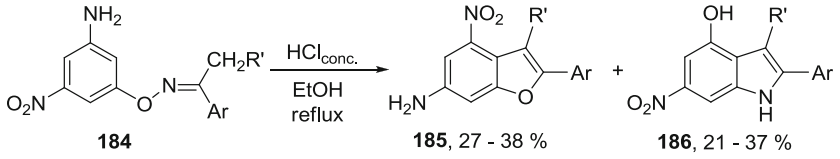
Each isomer can be isolated, using flash chromatography. In case of 2,4-dimethyl münchnone **178b** the reactions with 4- or 5-nitrobenzofurazans gave the same isoindole **181** (Scheme 88).



Scheme 88 1,3-Dipolar cycloaddition of 2,4-dimethylmünchnone to nitrobenzofurazans



Scheme 89 Cyclization of *O*-dinitrophenyl oximes



Scheme 90 Synthesis of 4-hydroxy-6-nitroindoles

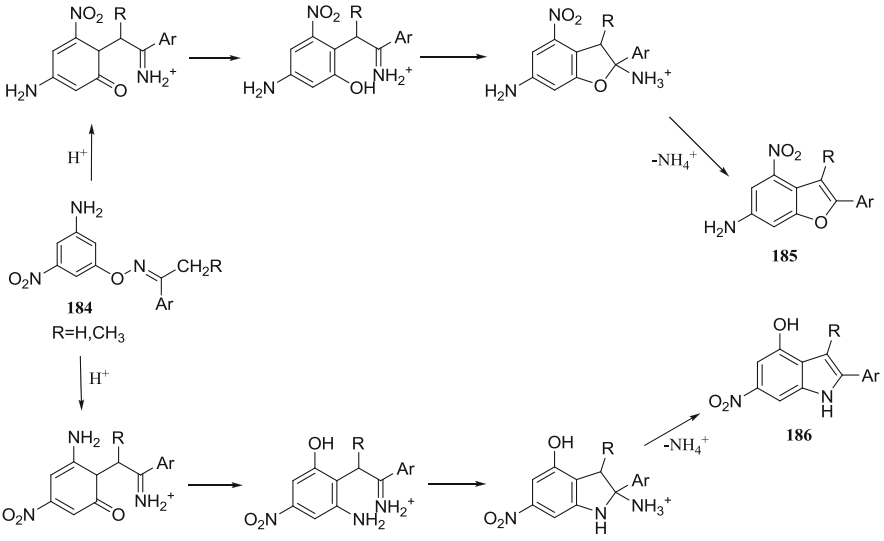
In summary, we have succeeded in developing a novel one-step method for the synthesis of isoindoles by annelation of the pyrrole ring to the benzene ring of nitroarenes.

6 Other Transformations

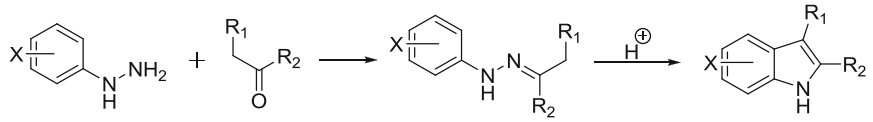
Aside from chemical transformations described above, there are some other approaches to the synthesis of nitrogen heterocycles using CH-functionalization of nitroarenes; among them an acid-promoted cyclization of *O*-nitrophenyl ketoximes **182** appears to be of particular interest [139] (Scheme 89).

The starting *O*-aryl oximes can be obtained through nucleophilic substitution of the nitro group in polynitrobenzenes. Heating these oximes under reflux in the presence of acids gives 4,6-dinitrobenzofurans **183** (Scheme 89). Reduction of one of two nitro groups in compounds **182** affords the corresponding nitroamines **184**. The cyclization of the latter in acidic media gives a mixture of 4-nitro-6-aminobenzofurans **185** and 4-hydroxynitroindoles **186** [140] (Scheme 90).

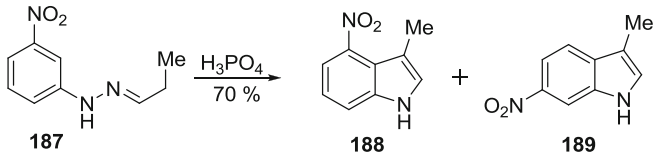
The authors suggested a plausible reaction scheme (Scheme 91) explaining the formation of both types of heterocycles.



Scheme 91 Proposed reaction scheme for the formation of 4-hydroxy-6-nitroindoles



Scheme 92 The Fisher indole synthesis

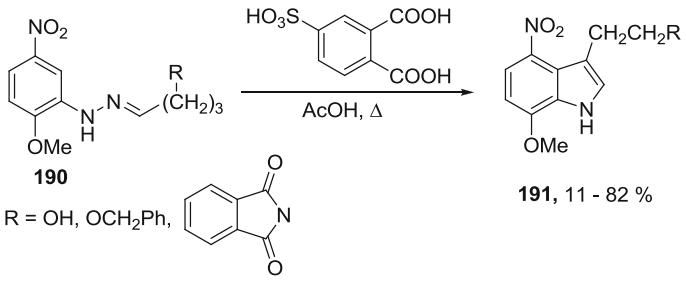


Scheme 93 Synthesis of isomeric nitroindoles

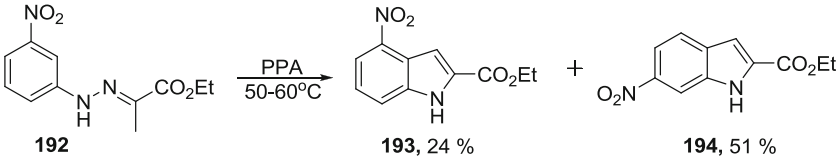
Another approach to N-heterocycles on the basis of nitroarenes is represented by cyclization of nitroaryl-substituted hydrazones of carbonyl compounds into indoles (Fisher indole synthesis) [141] (Scheme 92).

This cyclization is known to proceed smoothly, if electron-releasing substituents are present in the benzene ring of the intermediate hydrazones. Nevertheless, *meta*-nitrophenyl hydrazones of aldehydes and ketones undergo this reaction as well, although under more drastic conditions and in smaller yields.

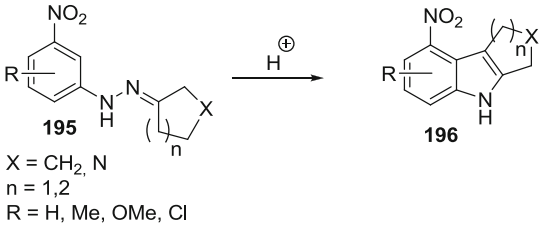
For example, heating 3-nitrophenyl hydrazone of propioaldehyde **187** in a mixture of toluene – 85% orthophosphoric acid gave rise to a hardly separable mixture of two regioisomers **188** and **189** (Scheme 93) in 70% overall yield [142].



Scheme 94 Synthesis of 4-nitroindoles



Scheme 95 The Fischer cyclization of ethyl pyruvate 3-nitrophenyl hydrazone



Scheme 96 Synthesis of condensed nitroindoles

When substituents in the *para*-position to the nitro group are present, the corresponding hydrazones afford the only possible isomer of indoles [143, 144] (Scheme 94).

3-Nitrophenyl hydrazones of ketones reacted similarly. On heating arylhydrazones of pyruvic ester **192** with polyphosphoric acid (PPA), mixtures of ethyl 4- and 6-nitroindole-2-carboxylates were formed [145, 146] (Scheme 95).

Hydrogenated derivatives of β-carboline [147], carbazole [148–150], and some other polycyclic systems [151–153] with the nitro group in the benzene ring (Scheme 96) were synthesized from hydrazones of cyclic ketones **195**.

The reactions have usually been carried out in the presence of sulfuric acid, PPA, or hydrogen chloride to give various products, depending on the structure of the starting hydrazones: if *para*-position to the nitro group is occupied, the only regioisomer has been obtained; otherwise mixtures of compounds are formed. This methodology has also been applied successfully to the synthesis of highly substituted indoles [154–157].

7 Conclusion

The survey of the literature data has shown that nitroarenes with unsubstituted *ortho*-position relative to the nitro group can be functionalized directly by using various types of C–H functionalizations to give nitrogen heterocycles or their precursors. The results presented in this chapter may provide a good basis for the directed synthesis of diversely functionalized nitrogen bi- and poly heterocyclic systems. The general features and plausible pathways for these chemical transformations have been described.

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