Nucleophilic Substitution of Hydrogen in Heterocyclic Chemistry

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1. Introduction

Nucleophiles can react with electron-deficient arenes in a variety of ways. The most important of them is addition to the ring to form anionic σ-adducts. There are two distinct cases of this process: (a) addition in positions occupied with leaving groups X such as halogens, alkoxy, etc., to form σ^X-adducts and (b) addition in positions occupied with hydrogen to form σ^H-adducts.

The σ^X-adducts formed in the former case undergo rapid elimination of X^-, giving products of nucleophilic aromatic substitution (S_NAr). This process known for many years is well recognized and properly treated in text books and monographs[1−4] and will not be addressed in this paper. Much more complicated is fate of the σ^H-adducts produced in the latter case. Since, with very few exceptions, direct departure of hydride anion does not occur readily, the σ^H-adducts dissociate to starting materials or enter a variety of transformations that lead to restoration of the aromaticity of the ring, giving products in which the hydrogen is replaced by the moiety of the nucleophile.[4−7]

There are a few early examples of reactions that undoubtedly proceed via addition of nucleophiles to electron-deficient arenes in positions occupied with hydrogen followed by transformations of the formed σ^H-adducts. Two such examples are shown in Scheme 1.

p-Chloronitrobenzene treated with KCN in aqueous ethanol gave *m*-chlorobenzoic acid—the process known as the von Richter reaction.[8−10] Reaction of this nitroarene with carbanion of phenylacetonitrile generated in the presence of KOH in aqueous ethanol gave 5-chloro-3-phenylbenzisoxazole, whereas in pyridine, an aprotic solvent, replacement of chlorine—S_NAr reaction—takes place.[11]

The first two reactions undoubtedly proceed via addition of the nucleophiles to *p*-chloronitrobenzene in the *ortho* position to produce σ^H-adducts and can be considered as replacement of hydrogen by a nucleophile, combined with other transformations. Taking into accounts that σ^{Cl}-adducts as intermediates in the replacement of Cl (Scheme 1, path 1c) are formed practically irreversibly, because the departure of Cl^- from the σ^{Cl}-adduct proceeds much faster than departure of the carbanion, the presented examples indicate that addition of these nucleophiles (cyanide and phenylacetonitrile anions) in positions occupied with hydrogen to give σ^H-adduct should proceed faster than addition in a position occupied with Cl. Despite these and some other reported examples of reactions proceeding via σ^H-adducts, generality of the

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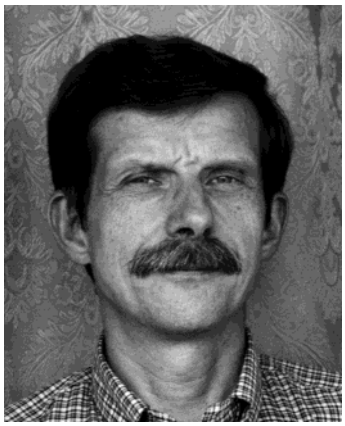

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process of nucleophilic substitution of hydrogen was not recognized, and these examples were considered as exceptions.

Only in the mid 1980s, mostly due to our studies,[5,12−15] it become evident that the addition of nucleophiles to electrophilic arenes in a position occupied by hydrogen to give σ^H-adduct is a fast process, as a rule faster than addition in similarly activated positions occupied with halogens. Thus, provided there are pathways for fast conversion of the σ^H-adducts into products of nucleophilic substitution of hydrogen, one should expect that this process that can proceed in a variety of ways could be a rich and promising field of organic synthesis.

The electron-deficient character of arenes, thus the ability to add nucleophilic agents, can be due to the presence of strongly electron-withdrawing substituents in the ring—most common is the nitro group, complexation of the ring with transition metals (typical examples are chromium tricarbonyl complexes of arenes)—or the electronic configuration of the ring itself as it is in azulene and in a variety of nitrogen heterocycles: 1,2,4-triazine, pyrimidine, etc. The electrophilic activity of heterocyclic azines is substantially amplified upon conversion into *N*-oxides. The general rule mentioned earlier that nucleophiles add faster in positions occupied with hydrogen than in those with other substituents holds for all kinds of electron-deficient arenes; thus, nucleophilic substitution of hydrogen should be a process feasible in all of these electron-deficient aromatic systems.

For discussion of various ways of conversion of the σ^H-adducts of nucleophiles to electron-deficient arenas, we will use nitrobenzene derivatives as the model arenes. In Scheme 1 it was shown that in the reaction of the phenylacetonitrile carbanion with *p*-chloronitrobenzene, addition in a position *ortho* occupied with hydrogen to produce σ^H-adduct should proceed faster than the addition resulting in formation of σ^{Cl}-adduct, whereas the latter adduct undergoes rapid conversion into the products via the departure of chloride anion. Extension of these conclusions to other nucleophiles implies that the addition to produce σ^H-adduct is a fast and reversible process; thus, the ultimate reaction course relies on relation of rates of formation of the σ^H-adduct, its dissociation, further conversion, and the rate of the competing formation of σ^{Cl}-adduct. Thus, for *p*-chloronitrobenzene, we can write a general reaction scheme, Scheme 2.

Pathways of further conversions of the σ^H-adducts are discussed below.

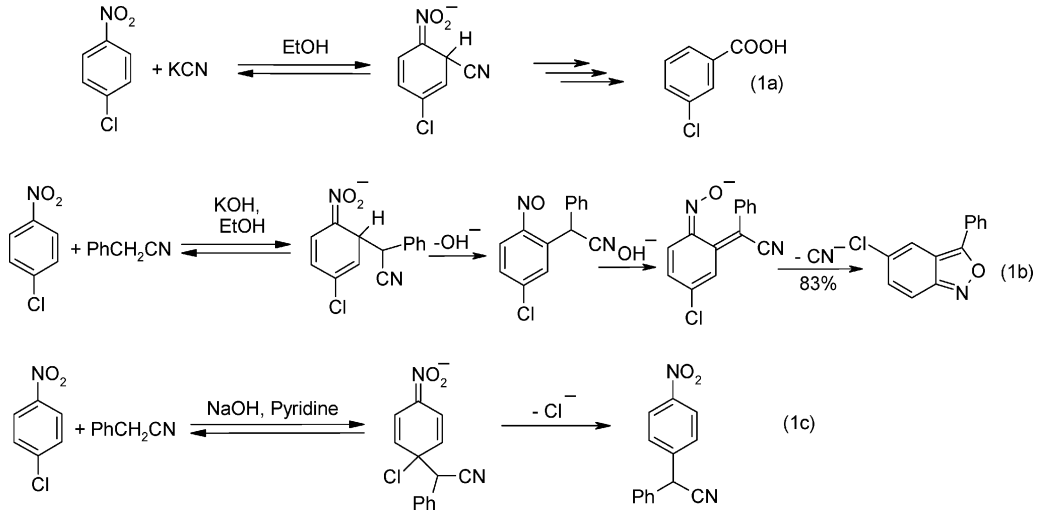
2. Pathways of Conversion of σ^H-Adducts

2.1. Oxidative Nucleophilic Substitution of Hydrogen

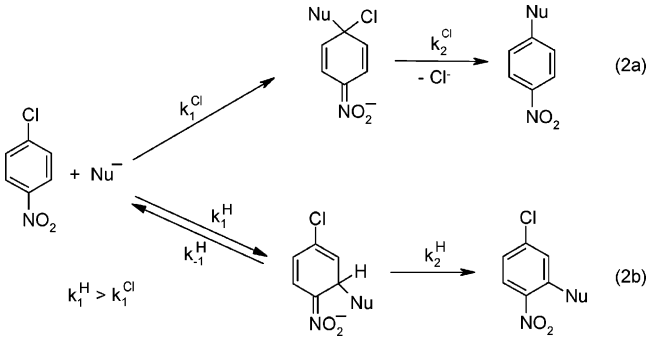
Direct conversion of such σ^H-adducts into products of nucleophilic substitution of hydrogen via spontaneous departure of hydride anion does not occur because it is of very low stability; therefore, the hydride anion needs to be removed by an additional reactant. This process is in fact equivalent to oxidation. Indeed, conversion of the σ^H-adducts via an oxidation with external oxidants is one of the major ways to afford nucleophilic substitution of hydrogen. For this process we proposed the term oxidative nucleophilic substitution of hydrogen (ONSH).[16−19]

Analyzing the feasibility of the process one should consider the rate of addition of a nucleophile to nitroarene ring k_1^H, position of the equilibrium k_1^H/k_{-1}^H, sensitivity of the nucleophile toward oxidation, and

Scheme 1



Scheme 2

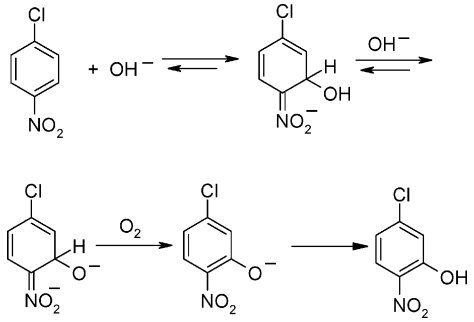


in particular nature of an oxidant. Since most of the nucleophilic agents are sensitive toward oxidation, one can formulate a priori guidelines concerning the feasibility of the ONSH process. The process should be feasible when[7] (a) nucleophiles are resistant toward oxidation, (b) the addition equilibrium is shifted toward σ^H-adducts due to high electrophilicity of the arenes, (c) the addition equilibrium is shifted toward σ^H-adducts because of high nucleophilicity or specific features of nucleophiles, and (d) specific oxidants are used to afford faster oxidation of the σ^H-adducts than nucleophiles.

Nucleophiles resistant toward oxidation are exemplified by hydroxide anion and ammonia. The ONSH with hydroxide anion is an old, well-known process occurring not only with nitroarenes but also with polycyclic electron-deficient arenes and heterocycles. The oldest example of the oxidative hydroxylation of nitroarenes is formation of picric acid from 1,3,5-trinitrobenzene via its reaction with sodium carbonate in the presence of potassium nitrate or potassium ferricyanide as oxidant.[20] Hydroxylation of nitrobenzene with solid sodium or potassium hydroxide gave variable yields (33−50%) of *o*-nitrophenol, with a small amount of *para* isomer.[21] The processes of direct oxidative hydroxylation with alkali metal hydroxides in which oxygen was the oxidizing agent were usually realized at elevated temperatures; thus, in the majority of older examples it was not possible to observe preference for the addition of hydroxide anions in positions with hydrogen, leading to σ^H-adducts and subsequently to ONSH over competing S_NAr of halogen when it was present in the *ortho*- or *para*-position of nitroarene. In fact, hydrolysis of *p*-chloronitrobenzene to *p*-nitrophenol with aqueous NaOH at high-temperature proceeding as S_NAr of the halogen is a well-known reaction.[22,23]

More detailed studies of this process have shown that at low temperature in liquid ammonia the rate of formation of the σ^H-adduct in the reaction of KOH with *p*- and *o*-chloronitrobenzenes is much higher than that of the σ^{Cl}-adduct and that oxidation of the former with oxygen is also a relatively fast process; thus, the ONSH takes place exclusively.[24,25] From some observations it also appears that oxidation of the σ^H-adducts of hydroxide anions is promoted by an excess of base and proceeds apparently with the deprotonated form of σ^H-adducts. For instance, under similar conditions, contrary to oxidative hydroxylation, ONSH with methoxide anion in *p*- and *o*-chloronitrobenzenes proceeds to a minor entent.[24,25] The

Scheme 3

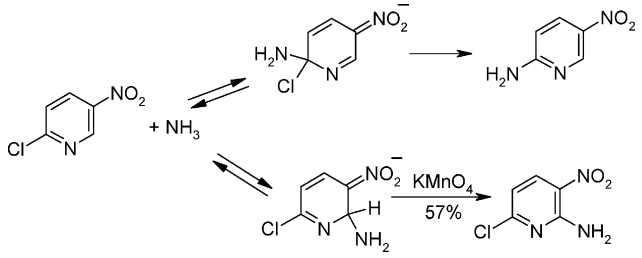


same reaction course with hydroxide anion is observed for bromonitrobenzenes; however, in the case of *o*- and *p*-fluoronitrobenzenes S_NAr of the halogen occurs exclusively. It is well known that S_NAr of fluorine proceeds much faster than chlorine. The preference for substitution of fluorine is particularly large in the case of oxygen nucleophiles; hence, the rate of addition of hydroxide anion in positions occupied with hydrogen seems to be lower than that in positions bearing fluorine ($k^{Cl} < k^H < k^F$).

Ammonia is a moderately active nucleophile, resistant at low temperature to $KMnO_4$, and a solution

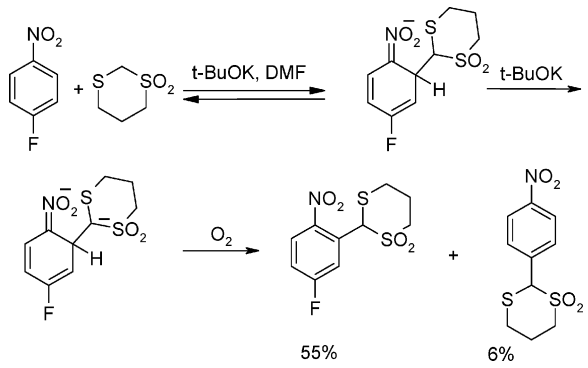
of $KMnO_4$ in liquid ammonia is an efficient system for oxidative amination of electron-deficient arenes. This solution, stable at the temperature of boiling NH_3, was introduced by van der Plas for oxidative amination of electron-deficient heterocycles such as 1,2,4-triazines, pyrimidines, nitropyridines, etc., with NH_3 or KNH_2—oxidative variant of the Chichibabin reaction.[26,27] Also, in this case preference for ONSH over S_NAr of halogen is observed (Scheme 4).[28]

Scheme 4



Particularly numerous are examples of ONSH processes in nitroarenes with carbon nucleophiles. These ONSH reactions with stabilized primary and secondary carbanions proceed often without intentionally introduced external oxidants.[5,6,19,29] It appears that in these cases dianions of σ^H-adducts are oxidized with oxygen always present in the system. Perhaps the most convincing exemplification of the tendency for such ONSH was observed in the reaction of *p*-fluoronitrobenzene with carbanion of 1,3-dithiane-1,1-dioxide (Scheme 5). Under conditions typical for

Scheme 5



such reactions, in DMF or liquid ammonia, at low temperature, and with an excess of base the ONSH strongly dominated over S_NAr of fluorine.[29]

To afford the S_NAr of fluorine in this system it was necessary to work in oxygen-free medium in DMSO using less than a stoichiometric amount of base. These results confirm the supposition that facile oxidation of the σ^H-adduct of the secondary carbanion was connected with its deprotonation; thus, the corresponding dianion was actually oxidized (Scheme 5). This observation is in good agreement with the results of oxidative hydroxylation where the reactions of nitroarenes with hydroxide anion led to the corresponding nitrophenols.[24,25]

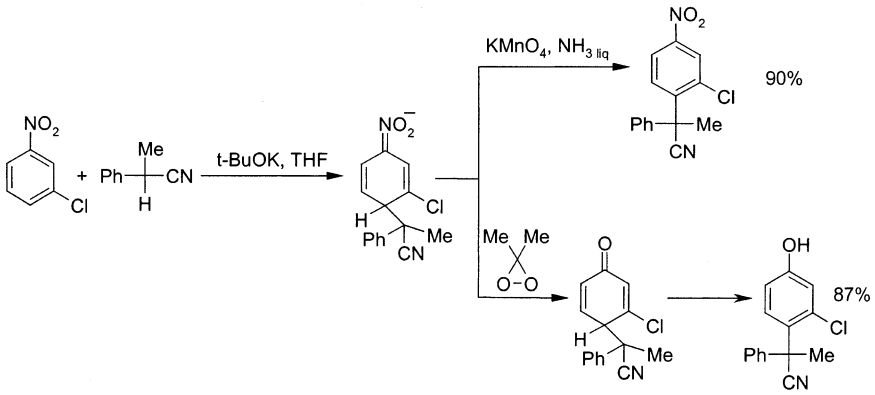
Similarly to σ^H-adducts of ammonia, those of carbon nucleophiles also can be efficiently oxidized by $KMnO_4$. In early examples of oxidative alkylation of nitroarenes with the Grignard reagents $KMnO_4$ was used as a solution in aqueous acetone.[30] We found that oxidation of the σ^H-adducts of the Grignard reagents and also of some tertiary carbanions to nitroarenes proceeds efficiently with $KMnO_4$ in liquid ammonia.[16−19,31,32] There are examples of use of salts of other metals on high degree of oxidation, chromium(VI),[33] cerium(III),[34] lead(IV),[35,36] and iron-(III),[36] for oxidation of σ^H-adducts of carbon nucleophiles, but usually they are less efficient and convenient than $KMnO_4$. Oxidation of such σ^H-adducts is also efficiently executed with quinone derivatives: chloranil and DDQ. In particular, the latter was shown to be an efficient oxidant converting σ^H-adducts into products of ONSH.[37−39]

There are many examples of oxidation of σ^H-adducts with bromine.[40,41] This reaction proceeds via an addition of bromine and elimination of HBr, so the overall stoichiometry is equivalent to an oxidation. Electrochemical oxidation of σ^H-adducts seems to offer interesting possibilities; however, the known examples are limited to σ^H-adducts of highly electron-deficient arenes, polynitroarenes,[42−46] or stable σ^H-adducts of the Grignard reagents.[47]

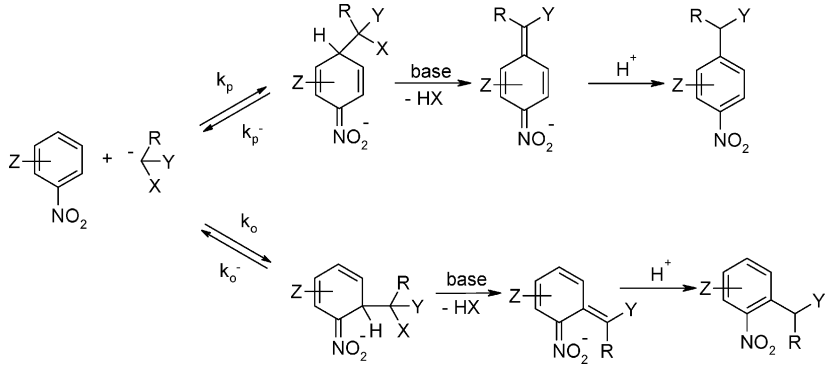
Oxidation processes presented above convert σ^H-adducts into products of replacement of hydrogen in electron-deficient rings with the moiety of the nucleophile. On the other hand, oxidation of σ^H-adducts of some carbanions to nitroarenes with dimethyldioxirane (DMD) gives different products—substituted phenols in which ring hydrogen is replaced with the nucleophile moiety whereas the nitro group is replaced by hydroxyl group.[48−50] The oxidation proceeds apparently via an attack of DMD on the negatively charged nitro group of the σ^H-adducts[48−50] and is related to the oxidative Nef reaction (Scheme 6).

Taking into account that oxidation of σ^H-adducts can be executed with a great variety of oxidants and also differences in the reaction course, one can suppose that there is no common mechanism for oxidation of σ^H-adducts with various oxidants. An interesting observation supporting this opinion came from comparison of the oxidation of σ^H-adducts of 2-phenylpropionitrile carbanion to substituted nitrobenzenes with different oxidants shown in Scheme 6.[16,18,48,51] The oxidation with $KMnO_4$ in liquid ammonia is strongly affected by substituents located in vicinity of the addition site (*meta* to the nitro group), apparently due to steric hindrance for approach of the oxidant. This supposition is supported by the high value of the kinetic isotope effect (KIE) $k^H/k^D \approx 9.7$ at −70 °C for this reaction, which indicates that breaking of the C−H bond is the rate-limiting step of this multistep process.[51] On the other hand, the oxidation with DMD is sensitive to steric effects of substituents *ortho* to the nitro group and proceeds without observable KIE ($k^H/k^D = 1$).[49] These observations indicate that permanganate anion and DMD interact directly with the respective oxidized sites. Contrary to this conclusion, detailed studies of electrochemical oxidation of σ^H-adducts using cyclic voltammetry have shown that the oxidation proceeds via stepwise transfer of electrons at various potentials.[44,45,47]

Scheme 6



Scheme 7



From the large variety of oxidants used in organic chemistry, only a few such, as molecular oxygen,[5,29] $KMnO_4$,[16−18] DDQ,[37,39,41] Br_2,[40] and dimethyl dioxirane,[48,49] have found wider application for oxidation of the σ^H-adducts. Very prospective is use of electrochemical oxidation for this purpose.[44−47] Oxygen is a very common oxidant for oxidation of the σ^H-adducts; it appears however that it operates efficiently only in the cases when σ^H-adducts can be further deprotonated by a base present in the system; thus, the corresponding dianion is actually oxidized.[24,25,29]

2.2. Conversion of σ^H-Adducts into Nitroso Compounds

Under proper conditions some σ^H-adducts undergo spontaneous conversion into substituted nitroso compounds. This reaction, due to its stoichiometry, can be considered as an intramolecular redox process with release of hydroxide anion. This conversion proceeds usually in protic solvents apparently via protonation of the negatively charged NO_2 group of the σ^H-adducts and elimination of water and is often followed by further transformations of the produced nitroso compounds.[11,52−56] The reaction shown in Scheme 1 (path 1b) proceeds along this pathway. Similar conversion can be promoted by treatment of σ^H-adducts with protic acids, Lewis acids,[57,58] or silylating agents.[59−62]

Nitrosoarenes produced in such processes are more active electrophiles than the starting nitroarenes; thus, as a rule, they enter further reactions that are dependent on the nature of nucleophile, nitroarene, and reaction conditions. Only in a few cases the nitrosoarenes or the corresponding tautomers, quinone oximes, can be isolated as such.[52,63,64] Often nitrosoarenes under the reaction conditions enter multistep transformations to heterocyclic systems,[57,58,60,65,66] as exemplified in Scheme 1 (eq 1b).[11]

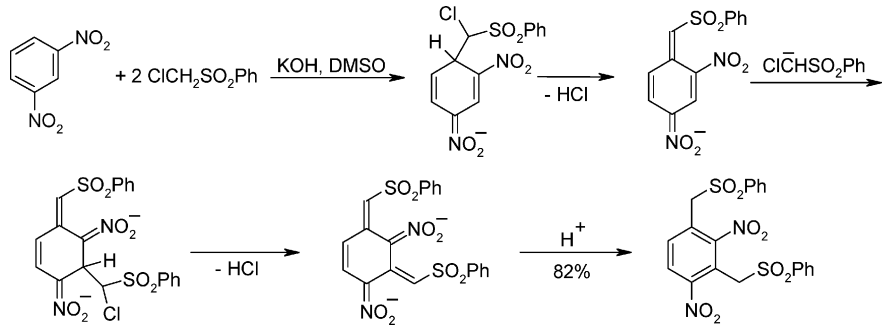
Oxidation of σ^H-adducts by external oxidants and their conversion according to the intramolecular redox stoichiometry to nitroso compounds offer interesting possibilities in organic synthesis, particularly chemistry of heterocycles; however, these processes are of limited scope and are often not predictable.

2.3. Vicarious Nucleophilic Substitution of Hydrogen

Perhaps the most general, predictable, and reasonably well-understood transformation of σ^H-adducts into products of nucleophilic substitution of hydrogen takes place when the reacting nucleophiles contain leaving group X at the nucleophilic center. The anionic σ^H-adducts formed via addition of such nucleophiles to nitroaromatic ring undergo base-induced β-elimination of HX to give anionic products, which upon protonation gave products of replacement of hydrogen with the nucleophile moiety. The general scheme of this reaction, named vicarious nucleophilic substitution (VNS),[13,15,67,68] for carbanionic nucleophiles is shown in Scheme 7.

The VNS reaction has found wide use for introduction of functionalized carbon substituents into nitroaromatic rings via the reaction of nitroarenes with α-halocarbanions and carbanions containing other leaving groups X, e.g., RO and RS, that can be eliminated as HX from the σ^H-adducts. The process is of general character: any carbanion in which X is

Scheme 8



as specified above can react with any nitroarene provided that at least one position *ortho*- or *para*- to the nitro group is occupied with hydrogen.[13,15,69] Some limitations can be due to mismatch of activities of partners and low stability of α-halocarbanions. For instance, highly stabilized carbanions of low nucleophilicity, such as those generated from dimethyl chloromalonate, do not react with moderately active nitrobenzene derivatives because of an unfavorable addition equilibrium and the very low concentration of σ^H-adducts but react efficiently with more active 2-nitrothiophene or nitrothiazole.[70] Trihalomethyl carbanions produced via deprotonation of chloroform and bromoform with t-BuOK undergo fast dissociation to dihalocarbenes; nevertheless, they afford dihalomethylation of nitrobenzene and more active nitroarenes but do not react with nitroanisole, because in the latter case the dissociation to dihalocarbene proceeds faster than the addition.[71] The same reaction proceeds with trichloromethyllithium.[72]

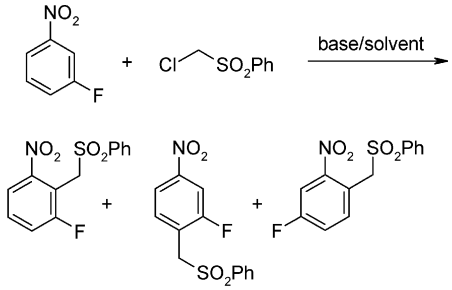
Products of the VNS reaction in nitroarenes exist in the reaction mixtures in the form of nitrobenzylic carbanions, unable to enter further nucleophilic addition; hence, the reaction proceeds selectively as monosubstitution. On the other hand, the reaction with polynitroarenes can result in a stepwise mono-, di-, and even trisubstitution because di- and trinitrobenzylic carbanions can behave as electrophilic partners in the reactions with carbanions (Scheme 8).[73,74]

The VNS reaction can often proceed in more than one position of a nitroaromatic ring, giving isomeric products. Orientation of the substitution depends on the kind of carbanion, substituents in the aromatic ring, and the reaction conditions.[15,75] Usually tertiary carbanions and secondary carbanions with bulky substituents and/or leaving group X react in the position *para* to the nitro group.

The orientation can often be controlled to a substantial extent by proper selection of the reaction conditions.[75−77] For instance, VNS with chloromethyl phenyl sulfone proceeds *ortho* to the nitro group when carried out in t-BuOK/THF system,[75] whereas in the presence of NaOH/DMSO a substantial amount of the *para* isomer is formed (Scheme 9).[75,78] Despite steric hindrances, tertiary carbanions of α-chloroalkyl sulfones at low temperature add predominantly *ortho* to the nitro group.[76]

The VNS reaction is a general process for replacement of hydrogen in electron-deficient aromatic rings with carbon substituents. Due to its generality and

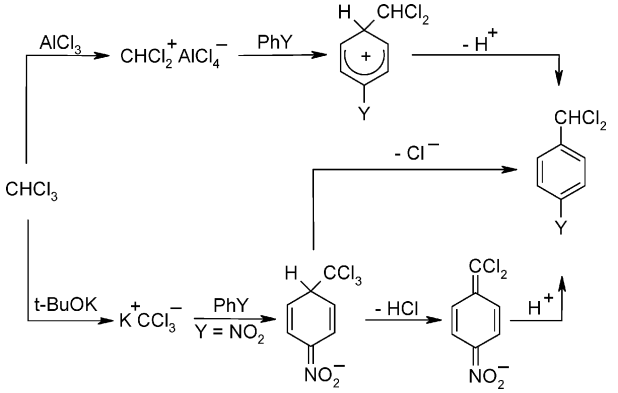
Scheme 9



base/solvent	total	A	B	C
NaOH/DMSO	86%	32%	57%	11%
t-BuOK/THF	90%	93%	0%	7%

stoichiometry, VNS can be considered as a process analogous to the Friedel−Crafts reaction, proceeding according to the opposite polarity. This can be exemplified by the reaction of arenes with chloroform promoted by $AlCl_3$ (Friedel−Crafts reaction) and strong base (VNS) (Scheme 10).[7]

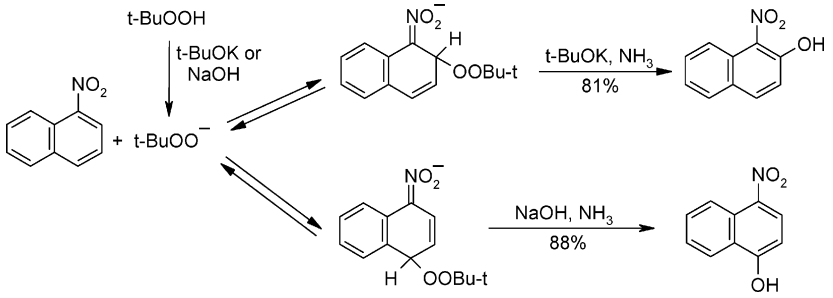
Scheme 10



Mechanistic features of the VNS reaction are relatively well clarified.[15,68,79−82] The reaction proceeds via two distinct steps: reversible addition of the carbanions to the nitroaromatic ring resulting in the formation of σ^H-adducts followed by base-induced β-elimination. Depending on the conditions, the addition or the elimination can be the slow, rate-limiting step of the overall process. In the latter case the reaction proceeds with significant kinetic isotope effects, $k^H/k^D > 1$, whereas in the former case the overall rate is limited by the addition step with secondary KIE, $k^H/k^D \approx 0.9$.[80,81]

Formation of the σ^H-adducts of α-halocarbanions to nitroarenes proceeds via direct nucleophilic addi-

Scheme 11



tion not via single electron transfer and combination of nitroaromatic anion−radical with radical. This conclusion came from numerous observations and direct experimental verification.[38,83]

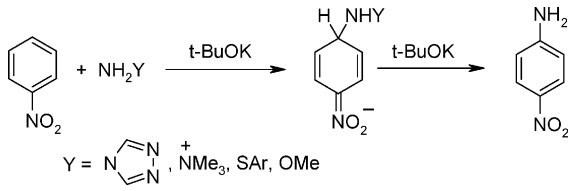
VNS is applicable also for introduction of hydroxy and amino substituents into electron-deficient aromatic rings. Anions of readily available alkyl hydroperoxides such as *tert*-butyl hydroperoxide and cumyl hydroperoxide add to nitroarene rings to produce σ^H-adducts which undergo base-induced β-elimination of the corresponding alcohol giving nitrophenolates.[77,84−86] Also, for this process it was shown that its rate is controlled by the concentration and strength of base, and often a significant KIE was observed. The effect of base on the rate of VNS hydroxylation is clearly shown in the reaction of bicyclic nitroarenes.[86] Nucleophilic addition to 1-nitronaphthalene proceeds faster in position 2 than 4, whereas the latter process produces better stabilized σ^H-adduct. Excess of strong base ensures fast β-elimination of the initially formed σ^H-adduct in position 2; hence, 2-hydroxy-1-nitronaphthalene is the main product in this case. On the other hand, in the presence of a weak base, β-elimination becomes a slower process than equilibration of the σ^H-adducts; thus, the reaction proceeds via the more stable σ^H-adduct in position 4, giving 4-hydroxy-1-nitronaphthalene (Scheme 11).[86]

Direct amination of nitroarenes with hydroxylamine has been known for more than 100 years,[87] but it has been limited to highly electron-deficient dinitroarenes[88−90] and nitronaphthalene.[91,92] Although the mechanistic pathway of this process was not clarified, it proceeds apparently according to the VNS mechanism. In recent years a few efficient aminating agents able to react with nitroarenes according to the VNS mechanism were developed.

The first examples of application of the VNS concept for amination of nitroarenes were reported by Katritzky.[93,94] In these examples 4-amino-1,2,4-triazole was used as aminating agent. Another hydrazine derivative 1,1,1-trimethyl hydrazonium iodide was found to be a mild and efficient aminating agent.[95−98] We developed a series of aminating agents—derivatives of sulfenamide.[99,100] Sumitomo chemists have shown that conversion of hydroxylamine into methoxyamine substantially increases its aminating power and scope of the reaction.[101−103]

From this short description it is evident that VNS offers wide possibility for replacement of hydrogen in electron-deficient arenes with functionalized carbon substituents, hydroxy and amino group; hence,

Scheme 12



it can be considered as a general and efficient tool in the synthesis of functionalized arenes.

In some cases σ^H-adducts of α-halocarbanions to electron-deficient arenes, particularly heterocycles, enter alternative transformations via intramolecular nucleophilic substitution of the halogen to produce three-membered rings of cyclopropanes and aziridines (Scheme 13).[79,104−108] This process, competing with the β-elimination leading to the VNS, is favored when negative charge generated on the ring due the addition of α-halocarbanion is not sufficiently delocalized; thus, the C or N atoms vicinal to the addition site exhibit highly nucleophilic character favoring intramolecular substitution, whereas base-induced β-elimination is hampered (Scheme 13).

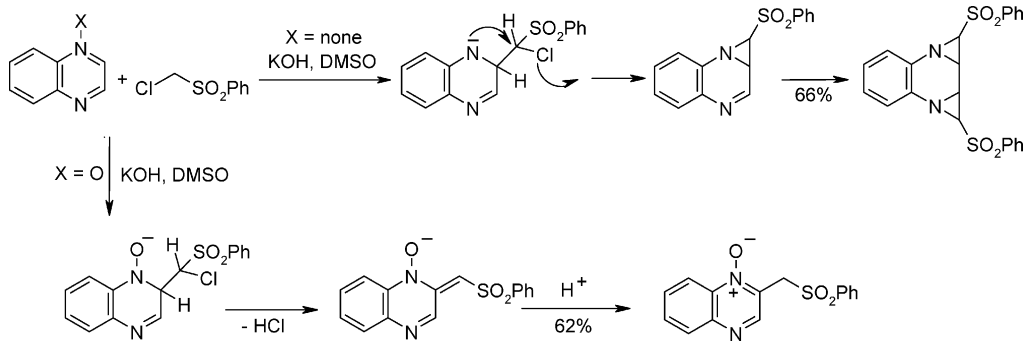
Structural modification of these electron-deficient arenes that promote more efficient delocalization of the negative charge in the σ^H-adducts (introduction of electron-withdrawing substituent, N-oxidation, etc) enable base-induced β-elimination and the VNS process (Scheme 13).[106]

It should be mentioned that the VNS of hydrogen proceeds also with electron-deficient alkenes.[109,110] Usually the γ-halocarbanions produced via addition of α-halocarbanions to the Michael acceptors enter intramolecular substitution resulting in formation of cyclopropanes; however, in some cases the base-induced β-elimination of hydrogen halide giving products of the VNS proceeds faster than the intramolecular substitution.

2.4. *Cine*- and *Tele*-Substiution

There are numerous examples of transformations of σ^H-adducts proceeding via departure of an anionic leaving group present in electron-deficient arenes from sites other than those to which a nucleophile was added. Disregarding mechanistic features of these processes, they can be divided into two groups. When the leaving group departs from a position vicinal to the addition site, the term *cine*-substitution is applied. On the other hand, when such a group departs from a more remote position of the ring or from a side chain, such processes are named *tele*-

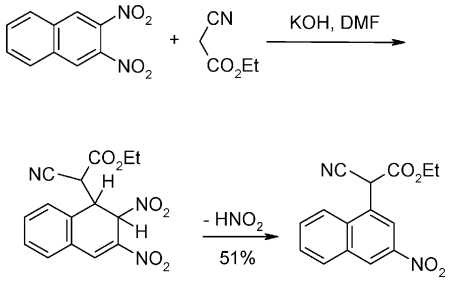
Scheme 13



substitution. The *cine*- and *tele*-substitution reactions in electron-deficient arenes were recently reviewed.[111]

Nucleophilic *cine*-substitution in carbocyclic nitroaromatic compounds, nitroheterocycles, and electrophilic heterocycles that do not contain nitro group have been reported in many papers. In the case of σ^H-adducts to polynitroarenes, one of the activating nitro groups could depart from the σ^H-adduct. For example, the reaction of 2,3-dinitronaphthalene with ethyl cyanoacetate in the presence of solid KOH in DMF results in the formation of ethyl cyano-2-(3-nitronaphth-1-yl)acetate (Scheme 14).[112] In this reac-

Scheme 14



tion the σ^H-adduct at position 1 undergoes base-induced elimination of nitrous acid, leading to the final product.

The *cine*-substitution was observed in reaction of 2,4-disubstituted nitrobenzenes with α-arylsulfonyl carbanions, also with those bearing a leaving group at the carbanionic center, when the reaction was performed at low temperature without additional base. Quenching of the formed σ^H-adduct with protic acid at low temperature resulted in formation of cyclohexadiene derivative that underwent spontaneous elimination of nitrous acid to form a product of *cine*-substitution (Scheme 15).[113]

Recently, examples of *tele*-substitution in the reaction of the Grignard reagents with 3-(trichloromethyl)nitrobenzene were reported (Scheme 16).[114]

An important approach to introduction of substituents into heterocyclic rings are reactions of nucleophiles with azine *N*-oxides particularly activated by alkylation,[115−117] acylation,[115−121] silylation,[122−125] etc., as, for example, in Scheme 17.[125]

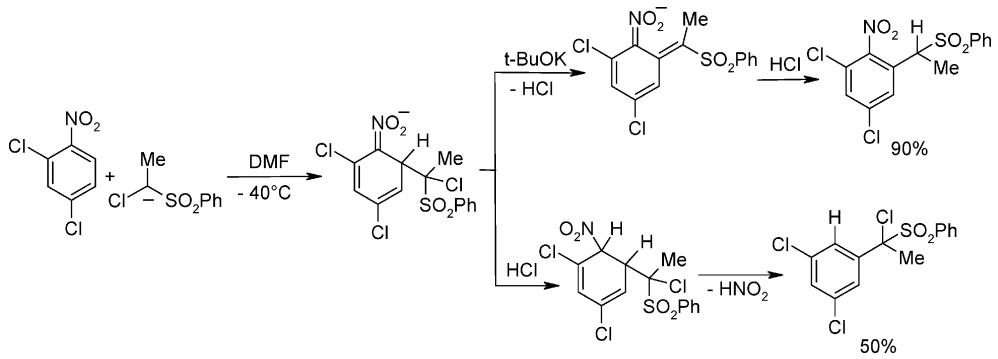
Although these reactions can be considered as substitution of hydrogen by *cine*- or *tele*-mechanisms, with the exception of a few examples, they will not be discussed in this paper because there are excellent comprehensive reviews of this field.[122−128]

2.5. Reactions Proceeding According to ANRORC Mechanism

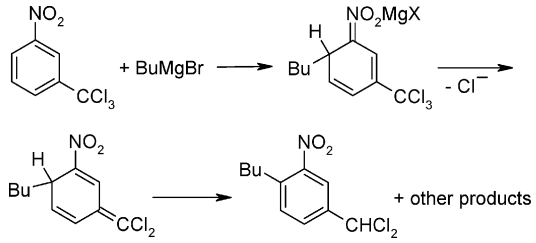
Treatment of some halogen-substituted heterocyclic compounds, such as chloro- and bromopyrimidines, with strong nucleophilic agents, e.g., amide anion, results in replacement of the halogen with amino group. Closer investigations of these reactions revealed, however, that they proceed via a multistep pathway that begins with the nucleophilic addition at positions occupied with hydrogen not the halogen. The σ^H-adducts formed undergo subsequent ring opening, elimination of HX producing cyano compounds, and intramolecular addition resulting in the ring closure, as shown in Scheme 18.[129,130]

This process, for which the term addition of nucleophile−ring opening−ring closure (ANRORC) was proposed, is of fairly general character and was thoroughly investigated by van der Plas. Detailed discussion of the scope, mechanism, and specific

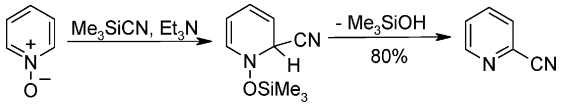
Scheme 15



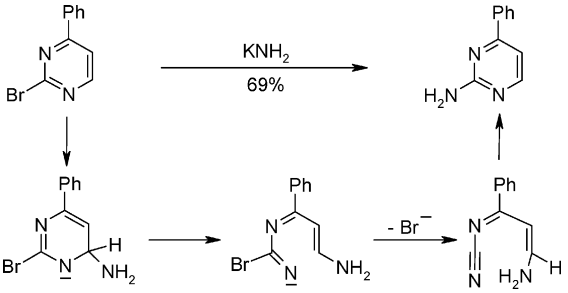
Scheme 16



Scheme 17



Scheme 18



features of the ANRORC reactions are published elsewhere.[131,132] For the purpose of this section it seems sufficient to stress that this is one of the major pathways among transformations of σ^H-adducts of strong nucleophiles to electrophilic heterocycles and that also in these systems nucleophilic addition in positions occupied with hydrogen occurs faster than in those occupied with halogens; thus, the ANRORC reactions can be considered as nucleophilic substitution of hydrogen proceeding as *tele*-substitution.

The numerous ways of conversion of σ^H-adducts of nucleophilic agents to electron-deficient arenes that lead to products of nucleophilic substitution of hydrogen, presented in this chapter, show generality and potential value of these reactions in organic synthesis. More detailed discussion of these reactions can be found in review papers[5,7,13−15,19,131−136] and monographs.[4,6]

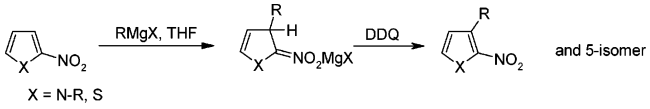
In this review we will show wide applications of these reactions in the synthesis of heterocyclic compounds. The presentation will be organized in the following way: first, we will present introduction of various substituents (carbon, nitrogen, oxygen, etc.) into existing electron-deficient heteroaromatic rings via nucleophilic replacement of hydrogen and then construction of a heterocyclic ring system (indoles, quinolines, etc.) utilizing these reactions. Finally, examples of total syntheses of natural products and biologically active compounds in which nucleophilic substitution of hydrogen is the crucial step will be presented.

3. Introduction of Substituents into Heteroarenes via Nucleophilic Substitution of Hydrogen

3.1. Alkyl Substituents

The Grignard and alkyllithium reagents add readily to electron-deficient heterocycles such as pyridine, quinoline, etc., to give respective dihydro compounds which are subsequently oxidized to the alkylated products.[36] The addition proceeds more readily to nitro derivatives of heterocyclic compounds.[63,64,137−140] For instance, alkylmagnesium bromides add to 1-alkyl-2-nitropyrroles and 2-nitrothiophene in both the activated 3- and 5-positions (Scheme 19). The pro-

Scheme 19



duced σ^H-adducts, upon treatment with DDQ, are oxidized to the corresponding alkyl nitropyrroles and thiophenes.[141]

2-Phenylethyl- and butylmagnesium chlorides add to 4-, 5-, 6-, and 7-nitrobenzothiazoles to form the respective σ^H-adducts, which upon oxidation with $KMnO_4$ or DDQ give alkylated nitroheterocycles.[30] Treatment of these σ^H-adducts with protic acids or BF_3 produces alkylated nitroso heterocycles,[137] whereas reduction with CuI gave the respective amino compounds (Scheme 20).[138]

Due to inequality of the bond order in bicyclic heteroarenes, addition of the Grignard reagents to nitro derivatives of these arenes proceeds predominantly *ortho* to the nitro group.[30,63,64,138,140,142]

Treatment of σ^H-adducts of Grignard reagents to some bicyclic nitroheteroarenes with sodium hypochlorite results in replacement of the nitro group with chlorine atom (Scheme 21). The reaction proceeds apparently via chlorination−nitrous acid elimination pathway.[142]

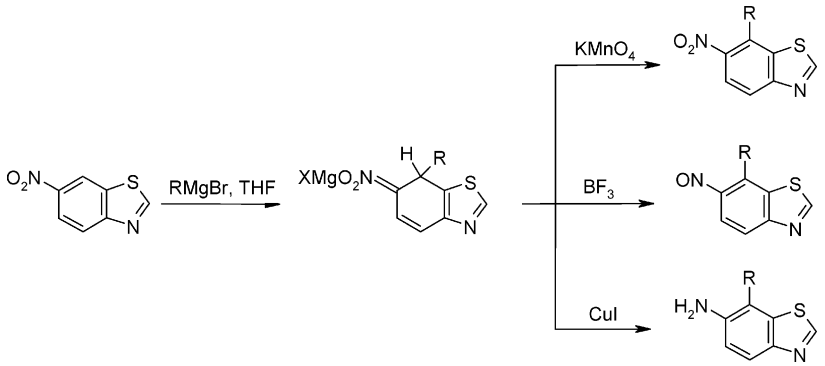
σ^H-Adducts formed from alkyl- and aryllithiums and quinoline *N*-oxides can be effectively oxidized with 9-fluorenone to form the corresponding 2-alkylquinoline *N*-oxides (Scheme 22).[36]

Although the concept of the VNS reaction was formulated in 1978,[67] there are a few early examples of alkylation of heterocycles with sulfone and sulfoxide carbanions proceeding undoubtedly according to the VNS mechanism. Russell found that quinoline, isoquinoline, benzisoxazole, acridine, and phenanthridine are readily methylated with dimsyl anion generated from DMSO in the presence of sodium hydride (Scheme 23).[143]

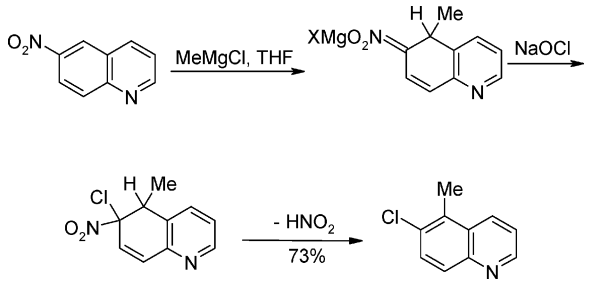
Similar results were obtained by Nozaki, who proposed for this process two mechanisms: sulfenate elimination or hydride transfer.[144] Benzoquinolines and their *N*-oxides undergo analogous process.[145] Dimsyl anion in the reaction with quinaldine gave mostly the tricyclic product of bis-addition, whereas the expected methylation was the minor process (Scheme 24).[146]

Nozaki described direct methylation of acridine with methyl phenyl sulfone and dimsyl carbanions.[147,148] Similarly, nitroarenes and nitroheteroarenes are alkylated via the VNS reaction with the carbanion of *n*-butyl trifluoromethyl sulfone (Scheme 25).[149] These processes can be considered as VNS reactions in which alkane− and arene−sulfonyl groups act as both carbanion stabilizing and leaving groups.

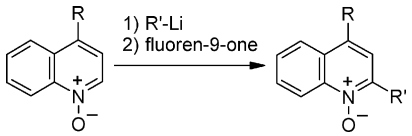
Scheme 20



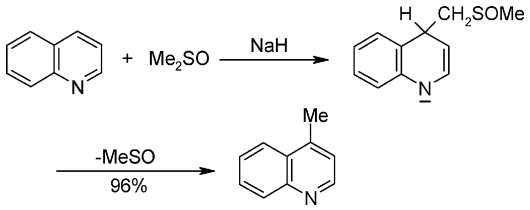
Scheme 21



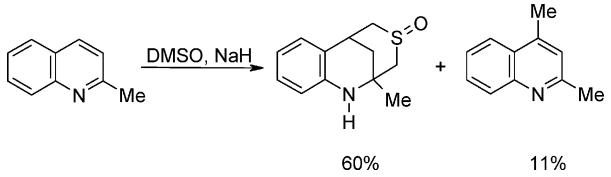
Scheme 22



Scheme 23



Scheme 24



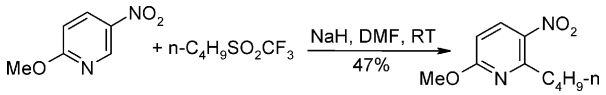
Highly electron-deficient heteroarenes (nitrobenzofuroxans and −furazanes) can be alkylated according to the VNS reaction protocol, even with nitronate anions via elimination of nitrous acid from the intermediate σ^H-adduct.[150]

Methylation of 1-benzenesulfonyl-2-nitroindole with lithium dimethylcuprate proceeds according to a *tele*-substitution mechanism (Scheme 26).[151]

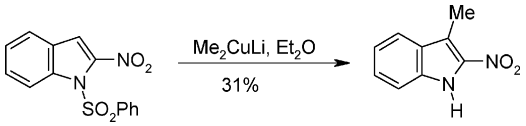
3.2. Alkenyl Substituents

Introduction of alkenyl substituents into nitroheteroarenes via direct nucleophilic replacement of hydrogen has not been reported. Alkenyl nitroheteroarenes can be readily prepared from nitroheteroarylmethanesulfones or sulfonic acid derivatives. Alkylation of these compounds with alkyl halides containing electron-withdrawing substituents is followed by base-induced β-elimination of sulfinic acid, giving (nitroheteroaryl)alkenes (Scheme 27).[152]

Scheme 25



Scheme 26



Heterocyclic analogues of nitrobenzyl sulfones undergo an $S_{RN}1$-type reaction with nitronate anions initiated by single electron transfer. The intermediate β-nitroalkyl arenes undergo elimination of nitrous acid as exemplified in the synthesis of vinylpyridine derivative (Scheme 28).[153] A relevant reaction of benzenesulfonylmethylimidazole anion with 2,2-dinitropropane furnishes vinylimidazole.[154]

3.3. Functionalized Alkyl Substituents

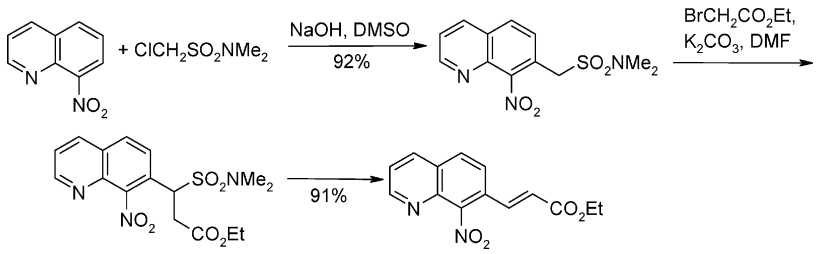
3.3.1. α-Haloalkyl Substituents

Monohalomethyl substituents can be introduced into some heterocyclic nitroarenes by direct halomethylation with dibromomethane or bromoiodomethane according to the VNS pathway, although due to the instability of the products in the reaction medium the scope of this reaction is limited.[155]

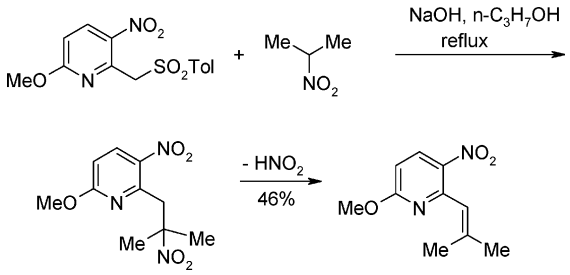
A much more convenient method of introduction of chloromethyl substituent seems to be the VNS reaction of nitroheteroarenes with *tert*-butyl dichloroacetate[156,157] followed by one-pot hydrolysis−decarboxylation of the produced *tert*-butyl α-chloro(nitroaryl)acetate (Scheme 29).[158]

Dihalomethyl derivatives of nitroheteroarenes are readily prepared by the direct VNS reaction with trichloro- and tribromomethyl carbanions[71,159] (Scheme 10). Nitro derivatives of furan,[71] pyrrole,[71] thiophene,[71] imidazole (Scheme 30),[71] pyridine,[71] indazole,[71,159,160] and quinoline[71] enter this reaction. Although dihalomethyl heterocycles are only of moderate stability in the reaction medium, they can be often obtained in excellent yields. Polyazaheterocycles, e.g., pte-

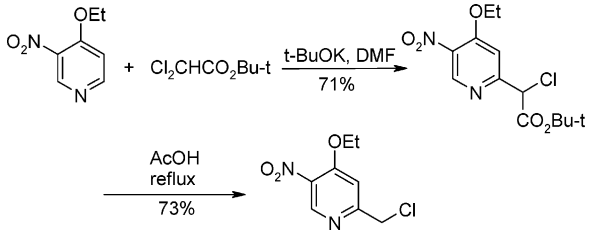
Scheme 27



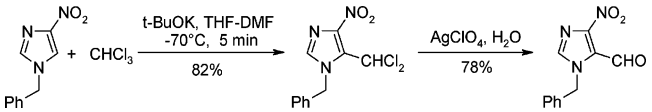
Scheme 28



Scheme 29



Scheme 30



ridines,[161] enter the VNS reaction with trichloromethyl carbanions without additional activation by an electron-withdrawing substituent.

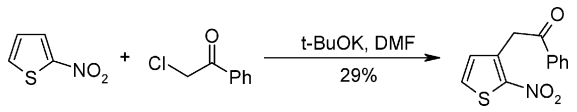
The dihalomethyl derivatives produced via the VNS reaction can be easily hydrolyzed to the corresponding aldehydes,[71,159] which are valuable starting materials for construction of condensed heterocycles, particularly pyrimidine derivatives (vide infra Scheme 134).

3.3.2. Ketones

α-Carbonylalkyl substituents can be introduced into heteroaromatic rings via ONSH with enolate anions or via VNS with enolates of α-chloroalkyl ketones. Quinoline *N*-oxide itself and its 4-chloro derivative react with enolate anions of ketones (methyl *tert*-butyl ketone, cyclohexanone, and acetophenone) to form products of the oxidative nucleophilic substitution of hydrogen in position 2.[162,163] It appears that intermediate σ^H-adducts are oxidized with oxygen. Silyl enol ethers activated by fluoride ion add to nitroarenes to give σ^H-adducts, which can be oxidized with bromine or DDQ to form α-(nitroaryl)-alkyl ketones.[37−39]

The VNS reaction in nitroarenes with α-chloroenolate anions furnishes arylmethyl ketones, as, for

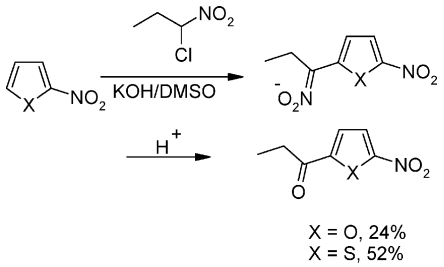
Scheme 31



example, in the reaction of 2-nitrothiophene with α-chloroacetophenone (Scheme 31).[164]

Acylation of 2-nitrofuran and 2-nitrothiophene was observed in the VNS reaction of these heterocycles with α-chloronitronate anions. The intermediate nitroarylnitronate anions underwent the Nef reaction, leading to the corresponding ketone (Scheme 32).[165]

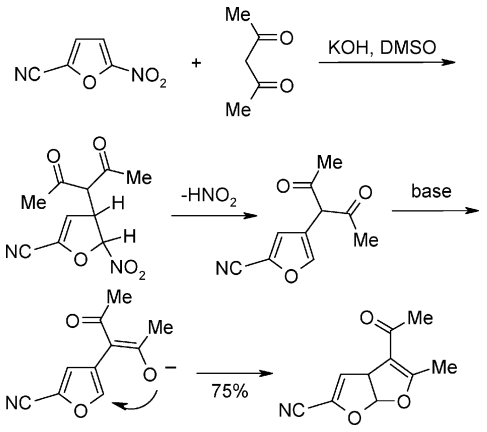
Scheme 32



X = O, 24%
X = S, 52%

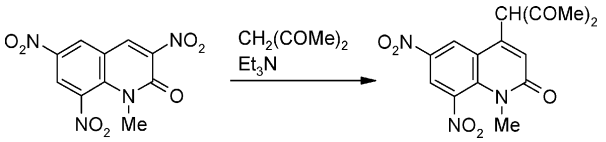
2-Nitrofuran derivatives containing electron-withdrawing substituents such as cyano or methoxycarbonyl group at position 5 add carbanions of *β*-dicarbonyl compounds in position 3, producing σ^H adducts that eliminate nitrite anion giving products of *cine*-substitution. Further intramolecular addition of intermediate enolate anion to the furan ring gave furo[2,3-*b*]furan skeleton (Scheme 33).[166]

Scheme 33



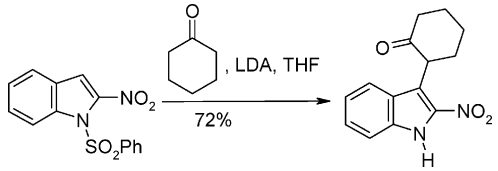
Acetylacetone reacts with 1-methyl-3,6,8-trinitroquinolin-2-one in the presence of trimethylamine to give the *cine*-substitution product in the heterocyclic ring (Scheme 34).[167]

Scheme 34



The reaction of lithium enolate of cyclohexanone with 1-benzenesulfonyl-2-nitroindole results in replacement of hydrogen in position 3, accompanied with elimination of benzenesulfonyl group in a process resembling *tele*-substitution (Scheme 35).[151]

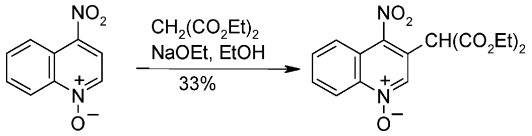
Scheme 35



3.3.3. Esters

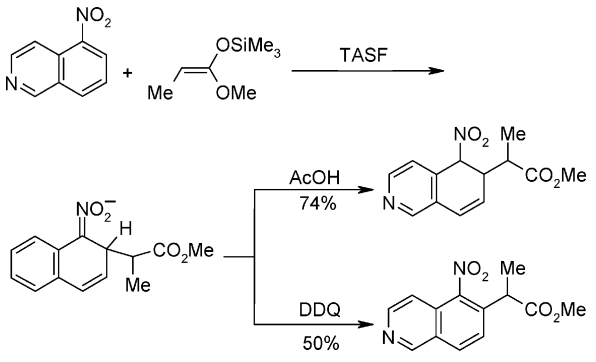
Alkoxycarbonylmethyl substituent can be introduced into quinoline *N*-oxide ring via oxidative nucleophilic substitution reaction with carbanions of alkyl acetates generated in the presence of strong base: t-BuOK or BuLi in liquid ammonia or *tert*-butylamine.[162] Similarly, σ^H-adduct of sodium diethyl malonate to 4-nitroquinoline-*N*-oxide undergoes oxidation, probably by the starting nitroarene, giving quinolylmalonate, although in moderate yield (Scheme 36).[168]

Scheme 36



Fluoride ion-induced reaction of ketene silyl acetals with 4- and 5-nitro-2,1,3-benzothiadiazoles,[38] 5-nitro-1,2,3-tiadiazole,[39] 5-nitroisoquinoline,[38] and 2-nitrothiophene[38] followed by oxidation with DDQ results in replacement of hydrogen in these heterocycles with the alkoxycarbonylalkyl group (Scheme 37).

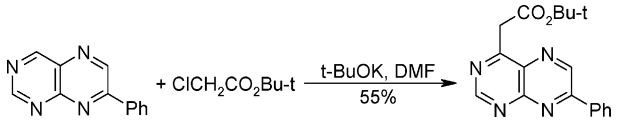
Scheme 37



Direct quenching of the σ^H-adduct with a proton source results in formation of isolable dihydro compound, which also can be oxidized to aromatic product.[38]

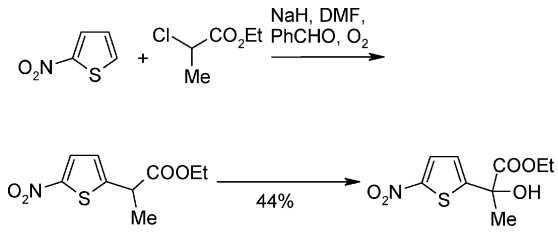
Carbanions of esters of α-chloroalkanoic acids react with aromatic nitro compounds according to the VNS scheme to form the corresponding esters of α-(nitroaryl)alkanoic acids.[169−174] 7-Phenylpteridine enters the VNS reaction with carbanion of *tert*-butyl chloroacetate to form 7-phenyl-4-*tert*-butoxycarbonylmethylpteridine (Scheme 38).[161]

Scheme 38



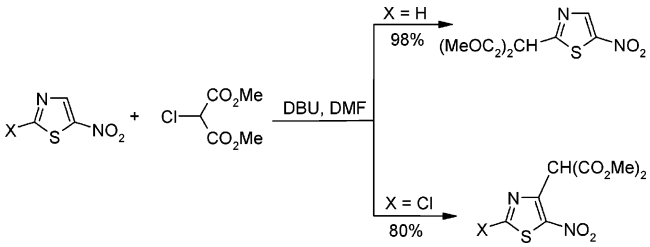
Oxidation of esters of nitroheteroarylalkanoic acids obtained via VNS provides the corresponding α-hydroxyesters (Scheme 39).[174]

Scheme 39



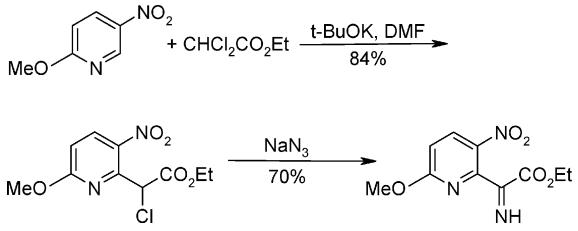
Although the carbanion of dimethyl chloromalonate is a weak nucleophile, it enters the VNS with 5-nitrothiazole in the presence of DBU in DMF replacing hydrogen in position 2 while in 2-chloro-5-nitrothiazole replacement of hydrogen in position 4 takes place (Scheme 40).[70]

Scheme 40



VNS reaction in nitroheteroarenes with alkyl dichloroacetates provides corresponding α-aryl-α-chloroacetates.[156,158] They are intermediates in the mentioned earlier indirect chloromethylation of electron-deficient arenes (Scheme 29).[158] Further functionalization is exemplified by treatment of these α-chloroheteroaryl acetates with sodium azide, resulting in formation of the corresponding imines (Scheme 41).[156]

Scheme 41

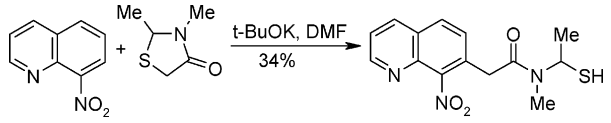


3.3.4. Amides

The carbanion of 2,3-dimethylthiazolidin-4-one enters the VNS reaction with 8-nitroquinoline via

heterocyclic ring opening, giving amides of nitroarylacetic acids (Scheme 42).[175]

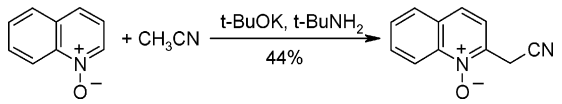
Scheme 42



3.3.5. α-Cyanoalkyl Substituents

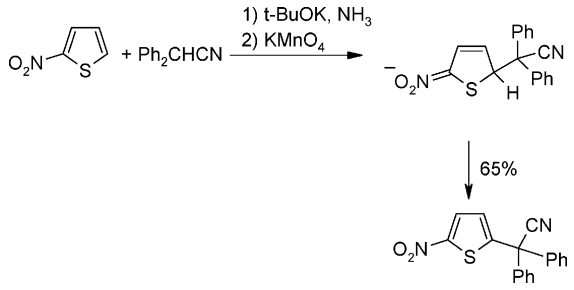
Cyanomethyl substituent can be introduced into electrophilic heteroarenes via oxidative and vicarious nucleophilic substitution of hydrogen. Oxidative cyanomethylation of quinoline *N*-oxide with acetonitrile carbanion reported by Hamana is probably effected by O_2 as the oxidant (Scheme 43).[162]

Scheme 43



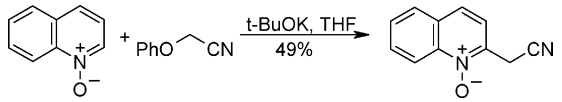
Tertiary carbanions of 2-phenylpropionitrile and diphenylacetonitrile due to steric reasons form the σ^H-adducts with nitroarenes only in the *para* or equivalent position to the nitro group. Oxidation of these σ^H-adducts with $KMnO_4$ leads to substituted nitriles (Scheme 44).[17]

Scheme 44



For cyanoalkylation of nitroarenes via the VNS reaction, carbanions of chloroacetonitrile,[176] aryloxyacetonitriles,[176−179] arylthioacetonitrile,[165,177] cyanomethyl dithiocarbamates,[165,177] or trialkylammonium cyanomethylides[180] are employed. Quinoline *N*-oxide enters VNS with phenoxyacetonitrile in the presence of KOH in DMSO or t-BuOK in THF to form the 2-cyanomethyl derivative (Scheme 45).[181]

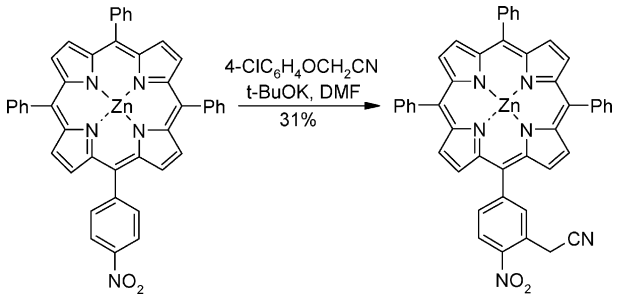
Scheme 45



Nitro derivatives of furan,[165] pyrrole,[165] imidazole,[182] thiophene,[165] pyridine,[178] indole,[183,184] and quinoline[185] undergo the VNS cyanomethylation reaction with a variety of cyanoalkylating agents listed above.

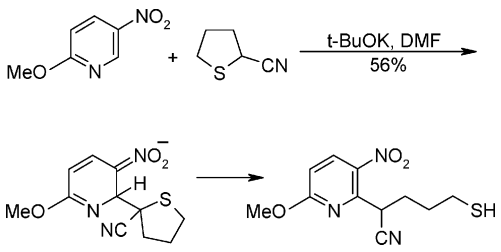
The cyanomethyl substituent can be introduced into a nitrophenyl ring connected to a porphyrin system via the VNS reaction with 4-chlorophenoxyacetonitrile (Scheme 46).[186]

Scheme 46



An interesting example of introduction of substituted cyanoalkyl substituent into nitropyridine is the VNS reaction of 2-methoxy-5-nitropyridine with the carbanion of 2-cyanotetrahydrothiophene proceeding via ring-opening β-elimination (Scheme 47).[175]

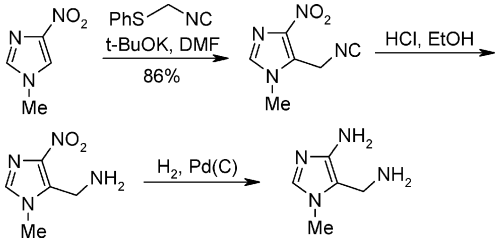
Scheme 47



3.3.6. Alkyl Substituents Containing Nitrogen in α-Position

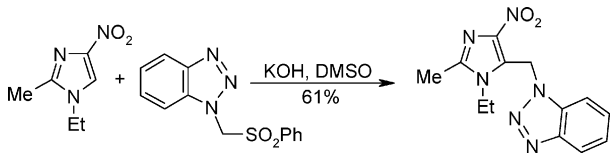
The isocyanomethyl group can be introduced into nitroheteroarene ring via the VNS reaction with the carbanion of phenylthiomethylisocyanide. Reaction of this carbanion with 2-nitrothiophene, 1-methyl-4-nitroimidazole, 2-methoxy-5-nitropyridine, and 5-nitroquinoline results in the replacement of hydrogen in the *ortho* position to the nitro group (Scheme 48).[187,188] The obtained products can be easily hydrolyzed to the respective formamides or amines.

Scheme 48



The carbanion of 1-phenylsulfonylmethylbenzotriazole adds to nitroheteroarenes to give σ^H-adducts that undergo base-induced β-elimination of benzenesulfinic acid producing benzotriazylmethyl derivatives (Scheme 49).[189]

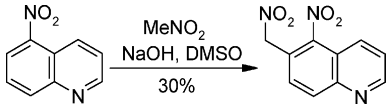
Scheme 49



Similar reactions proceed with other nitroheteroarenes: 4-nitropirazoles, 5-nitroindazoles, 5-nitrobenzotriazole, and 6-nitroquinoline.[189,190]

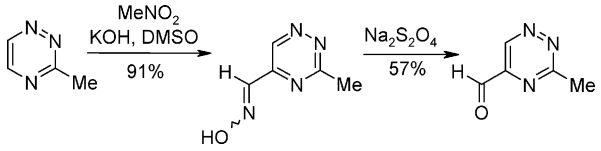
Nitromethane anion reacts with 5-, 6-, and 8-nitroquinolines giving the respective nitromethyl nitroarenes apparently via oxidation of the intermediate σ^H-adducts by air oxygen (Scheme 50).[191]

Scheme 50



In some cases σ^H-adducts of nitronate anions and electrophilic aromatic azines are converted into oximes.[192−194] For example, 3-methyl-1,2,4-triazine treated with nitromethane in the presence of solid KOH in DMSO undergoes conversion into oxime of 5-formyl-1,2,4-triazine (Scheme 51). The oxime can

Scheme 51



be cleaved with sodium dithionite to the respective aldehyde. Combination of these processes is an efficient way of direct nucleophilic acylation of this heterocyclic system.[193,194]

σ^H-Adducts of some nucleophiles and 5-substituted-2-nitrofurans often undergo elimination of nitrite anion giving products of *cine*-substitution. Thus, reaction of ethyl 5-nitrofuran-2-carboxylate with 2-nitropropane or nitrocyclopentane anions results mainly in the formation of 3-(α-nitroalkyl)-substituted furan derivative (Scheme 52).[195]

3.3.7. Alkyl Substituents Containing Sulfur in α-Position

Carbanion of 2-phenylthio-1,3-dithiane reacts with 2-chloro-3-nitropyridine according to the VNS scheme followed by a nucleophilic substitution of chlorine in the intermediate product produced phenylthiolate anion (Scheme 53).[196]

The VNS reaction of 2-methoxy-5-nitropyridine with ylide generated from mono-sulfonium salt of 1,3-dithiane proceeds via a ring-opening process (Scheme 54).[29]

As mentioned earlier, alkyl- and arylsulfonyl groups can undergo elimination from σ^H-adducts formed by α-sulfonyl carbanions.[144,147−149,197] However, when at the α-position of these carbanions, better leaving groups, e.g., Cl, are present; as in carbanions of α-chloroalkyl sulfones, the sulfonyl substituent remains in the product. In fact, carbanions of α-chloromethyl aryl sulfones are the most frequently used nucleophiles in the VNS reactions. Vicarious nucleophilic substitution is the reaction of choice for introduction of various α-sulfonylalkyl substituents into heteroaromatic ring.

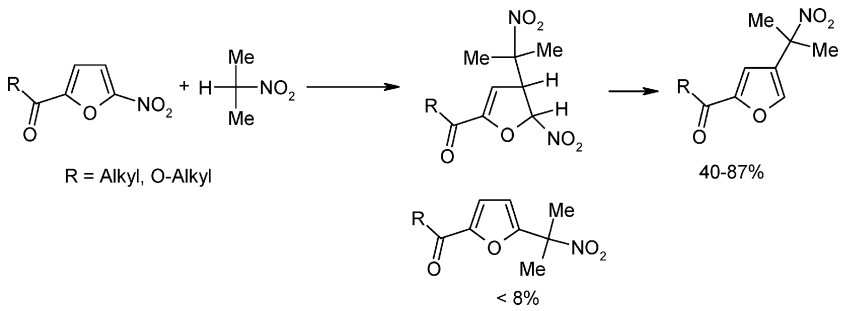
1,2,4-Triazines react with chloromethyl aryl sulfones and *N*,*N*-dialkyl chloromethane−sulfonamides to form products of VNS of hydrogen with sulfonylmethyl substituents in positions 3, 5, and 6 depending on the structure of the starting heterocycle.[198,199] Similarly, reacting benzothiazole,[200] benzoxazole,[200] and acridine[200] gives the VNS product in positions 2- and 9-, respectively. Pyridine and *N*-oxides undergo VNS of hydrogen in the reaction with chloromethyl sulfones.[181,201] Quinoline *N*-oxides react with chloromethyl phenyl sulfone in the presence of KOH in DMSO to form 2-phenylsulfonylmethyl derivatives.[181] In an analogous reaction, phenylthiomethyl tolyl sulfone forms variable amounts of both VNS and ONSH products, depending on the base−solvent system employed.[181]

The reaction of quinoxaline with carbanion of chloromethyl phenyl sulfone results in the formation of bis-aziridine (Scheme 13). Obviously the intermediate σ^H-adduct undergoes intramolecular substitution and this process is repeated.[106] On the other hand, when quinoxaline *N*-oxide was introduced in the reaction with the same carbanion the VNS product was formed in good yield (Scheme 13).[106] The reaction course in quinoxaline derivatives can be manipulated also by introduction of an electron-withdrawing group or replacing a carbon atom of the carbocyclic ring with nitrogen. This enhances susceptibility to the attack of nucleophile and favors formation of the VNS products due to more efficient delocalization of the negative charge in the intermediate σ^H-adduct.[79,106] This effect is observed in pyrido[2,3-*b*]pyrazine, which reacts predominantly according to the VNS scheme replacing hydrogen in the 3-position (Scheme 55).[106]

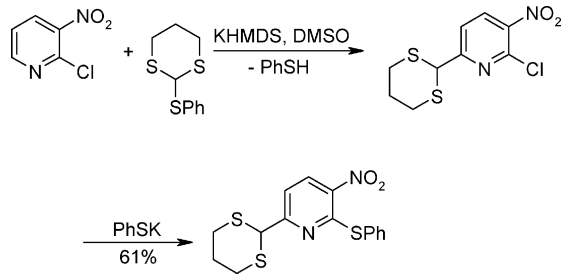
Pteridines enter the VNS reactions with chloromethyl aryl sulfones analogously as with alkyl chloroacetates shown in the Scheme 38.[161] Benzonaphthyridines react with chloromethyl phenyl sulfone to form annelated aziridines, while their mono- and di-*N*-oxides form VNS products (Scheme 56).[107,108]

N-Alkylpyridinium and other onium salts of azines, although very active electrophiles, do not react ef-

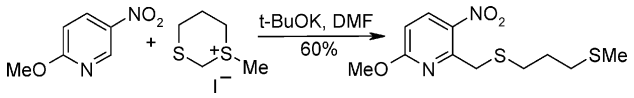
Scheme 52



Scheme 53



Scheme 54



ficiently with α-halocarbanions along the VNS pathway, perhaps due to instability of the intermediate adducts. On the other hand, dicyanomethylide derivatives obtained from pyridine[202,203] as well as analogous ylides of other azines (pyridazine,[204]1,2,3-triazine (Scheme 57))[203,205] are sufficiently activated toward nucleophilic substitution and react with chloromethyl phenyl sulfone replacing hydrogen in the position "*para*" to the activating group. Then the activating group can be easily removed by oxidation with ammonium persulfate in refluxing 2-propanol.

Numerous nitro derivatives of aromatic heterocycles (pyrrole,[165,206] furan,[165] thiophene,[165] pyrazole,[207] imidazole,[182] pyridine,[208,209] indole,[183] quinoline,[185] indazole,[210] benzotriazole,[211] quinoxaline,[79,106] porphyrins)[186] are active partners in the VNS reaction with carbanions of chloromethyl aryl sulfones, sulfonates, and sulfonamides, giving respective sulfonylmethyl derivatives, usually in excellent yields (Scheme 58).

3-Chlorobenzosultams generated in situ via halophilic reaction of an equimolar mixture of benzosultam and 3,3-dichlorobenzosultam[212] in the presence of solid NaOH in DMSO enter VNS substitution in nitroarenes and heteronitroarenes readily to form 3-aryl derivatives (Scheme 59).[213]

3.4. Reactions with Cyanide Anions

Reactions of cyanide anions with electron-deficient nitroarenes, including heteroarenes, often proceed in unexpected, peculiar ways, as, for example, the von Richter reaction (Scheme 1, eq 1a), and will be discussed separately. Cyano group attached to the ring increases its electrophilic activity, being itself susceptible toward nucleophilic attack, thus, the final outcome of these reactions depends on these effects.[112,214−222] In many instances reactions of cyanide anions with electron-deficient heteroarenes offer interesting possibilities. Nitroquinolines react with cyanide anions in a variety of ways, always the addition *ortho* to the nitro group being the initial step. 3-Nitroquinoline treated with potassium cyanide and an oxidant, potassium ferricyanide, in methanol gave 3-nitroquinoline-4-carbonitrile, the product of oxidative cyanation and aminoisoxazoloquinoline obviously formed via redox process and addition of the intermediate hydroxylamine to cyano group (Scheme 60).[214]

5-Nitroquinoline is converted by cyanide anions in methanol into a mixture of 6-cyano-5-methoxyquinoline, product of ONSH of hydrogen by CN and subsequent substitution of nitro group activated by cyano substituent by methoxy anion and 1-aminoisoxazolo[3,4-*f*]quinoline (Scheme 61).[215] The 3-, 5-, and 7-nitro-substituted quinolines reacted similarly.[215]

The reactions of nitroquinolines with cyanide ion and additional nucleophile (ethyl cyanoacetate[218,220−222] and ethyl nitroacetate)[222] in the presence of KOH produce derivatives of aminocyanoarenes. In these reactions the intermediate σ^H-adducts of cyanide anion are presumably converted into the cyanonitrosoarenes, which undergo further transformations including condensation of the active methylene compound with the nitroso group followed by conversion of the formed imine (Scheme 62).[219]

4-Nitroquinoline *N*-oxide reacts with ethyl cyanoacetate in the presence of potassium cyanide in DMSO to form (3-cyanoquinol-4-yl)cyanoacetate (Scheme 63).[216] The reaction proceeds as an oxidative substitution of hydrogen by a cyanide anion followed by nucleophilic replacement of the nitro group with cyanoacetate moiety.

3.5. Amination

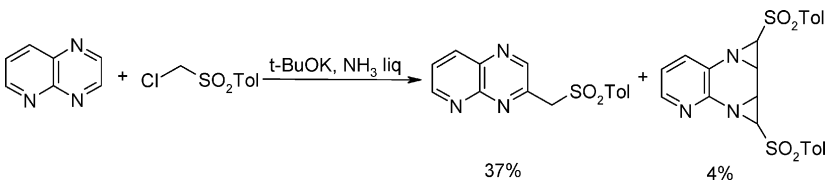
Amination of electron-deficient heteroarenes (pyridine, quinoline) and some other heterocyclic azines with sodium or potassium amides, known as the Chichibabin reaction, is an infrequent example of a process of nucleophilic substitution of hydrogen proceeding via departure of hydride anion from the intermediate σ^H-adduct (Scheme 64).[223−225]

This reaction has found numerous synthetic applications and is a process of great practical value being executed commercially for production of 2-aminopyridines and -quinolines. Pyridine and some other azines react also with metalated hydrazines and alkylhydrazines to give the corresponding heteroarylhydrazines in a process analogous to the Chichibabin reaction (Scheme 65).[226]

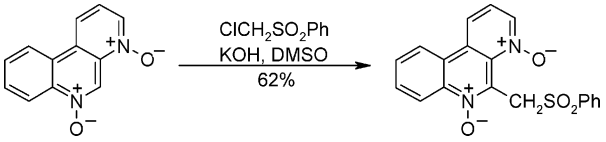
The detailed discussion of the mechanism, scope, and limitations of Chichibabin reaction can be found in review articles.[224,225]

σ^H-Adducts of ammonia or amide anions to azines are readily oxidized with a solution of $KMnO_4$ in

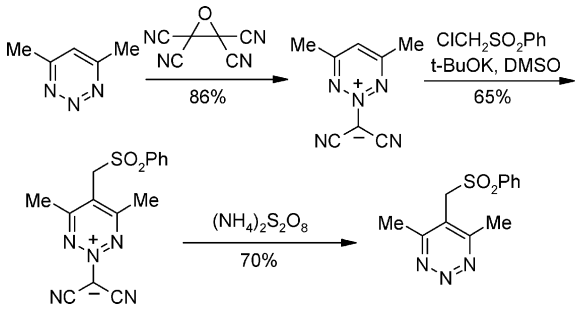
Scheme 55



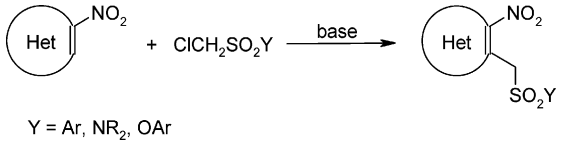
Scheme 56



Scheme 57

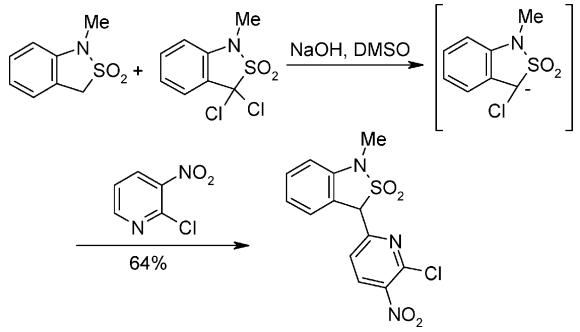


Scheme 58

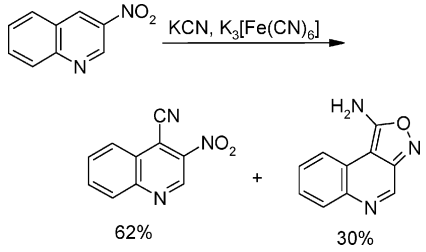


Y = Ar, NR_2, OAr

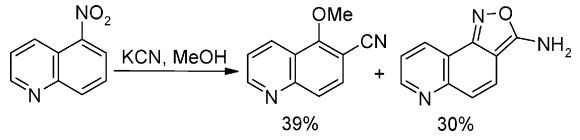
Scheme 59



Scheme 60

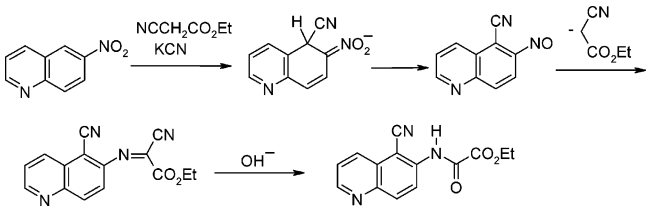


Scheme 61

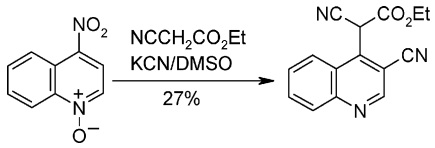


liquid ammonia to produce aminoheterocycles. This protocol, known as the oxidative Chichibabin reaction, was introduced to practice of organic synthesis by van der Plas.[27] For highly electrophilic heteroarenes such as naphthyridines,[133] 1,2,4-triazine (Scheme 66),[26] etc., ammonia itself is a sufficiently strong nucleophile able to form σ^H-adducts, thus, simple dissolution of such arenes in a solution of

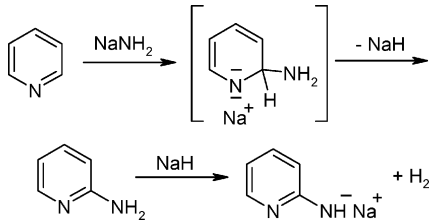
Scheme 62



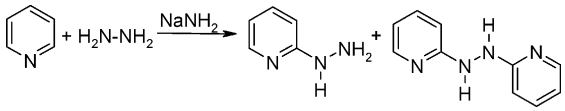
Scheme 63



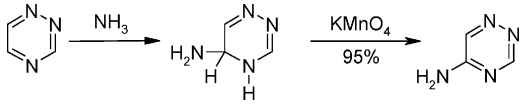
Scheme 64



Scheme 65



Scheme 66



potassium permanganate in liquid ammonia results in introduction of amino group via ONSH.

In a similar reaction, 3-nitropyridine gives a mixture of all three expected 2-, 4-, and 6-amino-3-nitropyridines.[28,227,228]

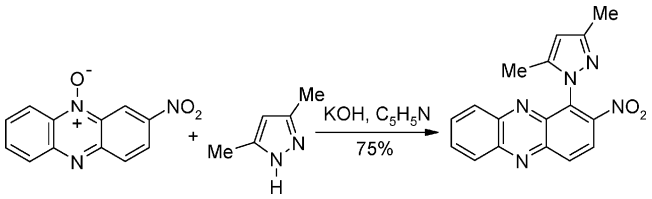
In the case of less electrophilic arenes, ammonia does not form σ^H-adducts in sufficient concentration; thus, sodium or potassium amide should be used as the aminating agent. It should be stressed that as in the cases of ONSH with hydroxide anion, oxidative amination proceeds faster than conventional S_NAr of chlorine or bromine when they are present in the ring of electrophilic heteroarene (Scheme 4).[28]

Treatment of electron-deficient heteroarenes with a solution of $KMnO_4$ in methylamine results in direct introduction of NHMe substituent via ONSH reaction.[28,229]

There are some examples of intramolecular oxidation of the σ^H-adducts of *N*-anions of heterocycles by the *N*-oxide functionality, located in the vicinity of the addition site as in the reaction of pyrazole derivative with 2-nitrophenazine-5-oxide (Scheme 67).[230,231]

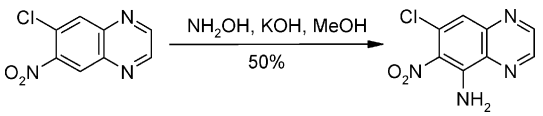
Amination of nitroarenes and nitroheteroarenes with hydroxylamine in basic media, known for more than 100 years,[87] is limited to highly electrophilic arenes such as *m*-dinitrobenzene and bicyclic nitroarenes. Although the mechanistic feature of this

Scheme 67



reaction was not recognized, it proceeds apparently according to the VNS scheme. Amination of 3-, 5-, 7-, and 8-nitroquinolines with hydroxylamine in the presence of potassium hydroxide in methanol gives the corresponding 2-, 8-, 8-, and 5-amino derivatives.[232] Under similar conditions (Scheme 68), ami-

Scheme 68

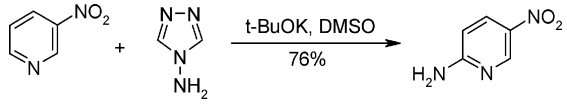


nation of 3-nitropyridine[227] and 5-chloro-7-nitroquinoxaline proceeds successfully.[233]

1,2-Dimethyl-4-(and -5-)nitroimidazoles react with hydroxylamine in the presence of KOH to form respective 5- and 4-amino derivatives.[234] There are also examples of amination of pyridazinones with hydrazine.[235]

Although in the presented examples amination of electron-deficient heteroarenes proceed undoubtedly via VNS pathway, intentional application of the VNS concept to amination of electron-deficient arenes was initiated by Katritzky, who introduced 4-amino-1,2,4-triazole as an aminating agent.[93,94] This reaction proceeds in the presence of t-BuOK, obviously via deprotonation of the amino group, addition of the anion to an arene, followed by β-elimination of triazole. This reagent was applied to amination of nitropyridines and 4-nitroisoquinoline (Scheme 69).[227]

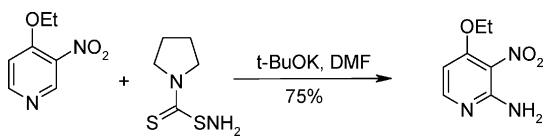
Scheme 69



Numerous other hydrazine and hydroxylamine derivatives, such as 1,1,1-trimethylhydrazinium iodide,[95,96] methoxyamine,[101−103] and a variety of sulfenamides,[99,100] were subsequently developed as efficient aminating agents according to the VNS protocol.

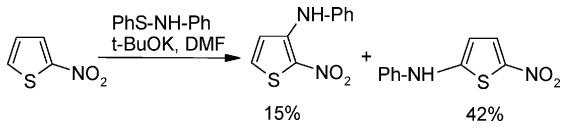
Amination of five- and six-membered heterocycles with *N*-tetramethylenethiocarbamoylsulfenamide proceeded satisfactorily. 4-ethoxy-3-nitropyridine and 2-methoxy-5-nitropyridine were aminated in the 2 position (Scheme 70).[100]

Scheme 70



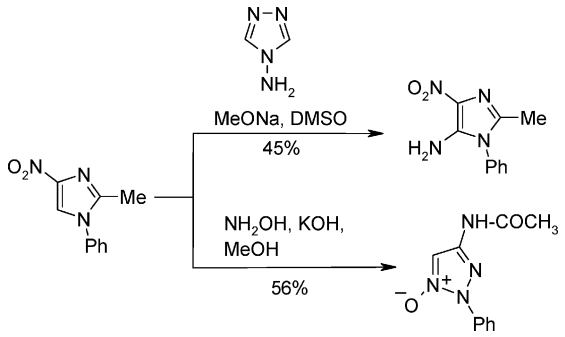
In 1,2-dimethyl-5-nitroindole and 6-nitroquinoline, replacement of hydrogen in the reaction with this reagent takes place in the benzene ring to produce the corresponding 4-amino-5-nitroindole and 5-amino-6-nitroquinoline.[100] 2-Nitrothiophene with benzenesulfenanilide formed a mixture of 3- and 5-phenylamino-2-nitrothiophenes in which the latter prevails (Scheme 71).[100]

Scheme 71



1-Phenyl-4-nitroimidazoles react with 4-amino-1,2,4-triazole in DMSO according to the VNS amination scheme to form the corresponding 5-amino derivatives, while the reaction with hydroxylamine in methanol gave triazole *N*-oxide (Scheme 72).[236,237]

Scheme 72

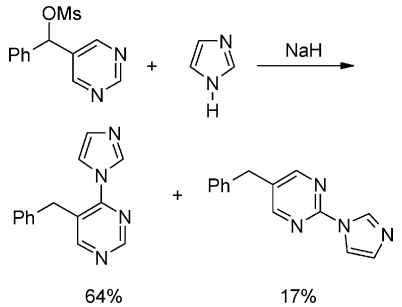


Apparently in the latter case the initially formed σ^H-adduct does not undergo fast elimination of water, so an ANRORC process instead of the VNS takes place.[237]

Numerous examples of reactions resulting in replacement of hydrogen in electron-deficient heteroarenes with amino group that proceed according to the *cine*- and *tele*-substitution mechanisms were recently reviewed.[111]

For instance, the reaction of imidazole anion with 5-(α-mesyloxybenzyl)pyrimidine proceeds via its addition in positions 4- and 2- of the pyrimidine ring followed by elimination of mesylate anion, giving products of the *tele*-substitution (Scheme 73).[238]

Scheme 73

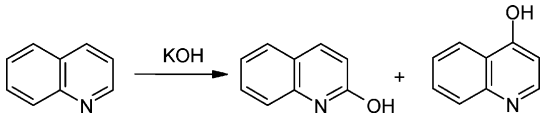


Analogous reaction proceeds with pyrrole and indole anions. In the reaction of 5-mesyloxymethylpyrimidine with indole anion, besides *tele*-substitution, also nucleophilic substitution of the mesyl group takes place.

3.6. Hydroxylation

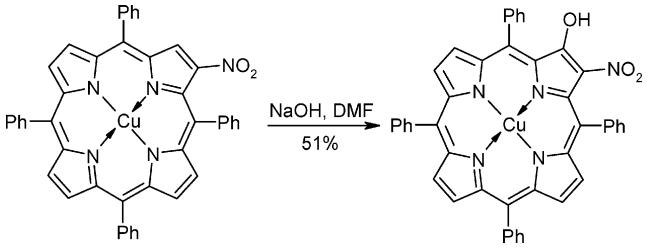
Quinoline can be directly hydroxylated in the reaction with potassium hydroxide at elevated temperature according to the ONSH pathway (Scheme 74).[239,240]

Scheme 74



The reaction of 2-nitro-5,10,15,20-tetraphenylporphyrin with sodium hydroxide in DMF results in hydroxylation of the pyrrole ring (Scheme 75).[241]

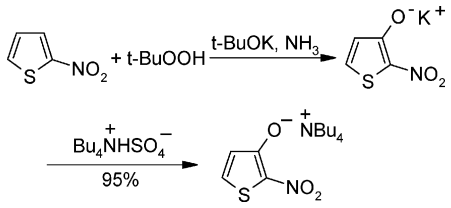
Scheme 75



Similar reactions with sodium methoxide resulted in formation of the corresponding methyl ether.[241]

Hydroxy substituents can be introduced into nitroarenes and nitroheteroarenes by the VNS reaction with anions of *tert*-butyl hydroperoxide or cumyl hydroperoxide. Usually the products, nitrophenols, are obtained in high yields and the orientation of substitution can be controlled by the reaction conditions (Scheme 12).[77,86] Since alkyl hydroperoxide anions exhibit moderate nucleophilicity, the reaction proceeds satisfactorily only with nitroheteroarenes of rather high electrophilicity. Thus, hydroxylation of 2-nitrothiophene with potassium *tert*-butyl hydroperoxide proceeds exclusively at the 3 position, giving relatively unstable 3-hydroxy-2-nitrothiophene, which can be isolated as a stable, crystalline tetrabutylammonium salt (Scheme 76).[86]

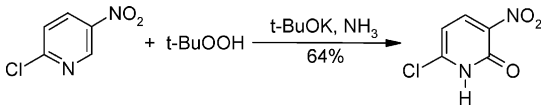
Scheme 76



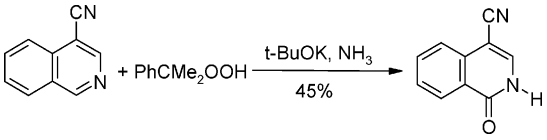
Replacement of hydrogen with hydroxy group in nitropyridines via the VNS reaction with *tert*-butyl hydroperoxide gives expected nitropyridones.[86] The VNS hydroxylation of 2-chloro-5-nitropyridine is the exclusive process, and competing nucleophilic substitution of the labile halogen was not observed (Scheme 77).[86]

Under analogous conditions, from 6-nitroquinoline solely 5-hydroxy derivative was formed, while in the case of 8-nitroquinoline, the reaction course is dependent on the character of the used base. Analogously, as in the case of 1-nitronaphthalene shown in the Scheme 11, hydroxylation of 8-nitroquinoline in the presence of NaOH and t-BuOK took place in positions 5 and 7, respectively.[86] Due to the higher activity of the bicyclic system in nucleophilic addition, even isoquinoline activated by cyano group, 4-cyanoisoquinoline, reacts with cumene hydroperoxide to form the product of substitution of hydrogen at position 1, albeit in moderate yield (Scheme 78).[86]

Scheme 77

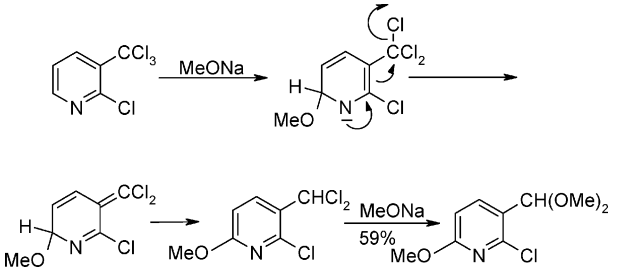


Scheme 78



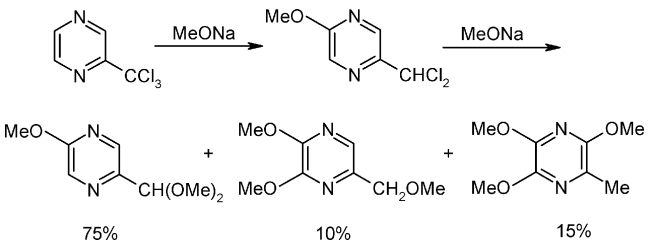
Electron-deficient heteroarenes bearing di- and trihalomethyl substituents react with alkoxides according to the *tele*-substitution pathway giving products of substitution of the ring hydrogen by alkoxy group. This process is followed by substitution in the dichloromethyl or chloromethyl group with alkoxides leading to the corresponding acetals or ethers.[242−245] For example, the reaction of 2-chloro-3-trichloromethylpyridine with an excess of sodium methoxide results in formation of dimethylacetal of 2-chloro-6-methoxypyridine-3-carbaldehyde (Scheme 79).[246]

Scheme 79



In some instances, polysubstitution of hydrogen in the ring takes place as in the reaction of 3-dichloromethylpyrazine with 3-fold excess of sodium methoxide, which results in quantitative formation of a mixture of three products (Scheme 80).[247] 2-Chloro-3-dichloromethylpyrazine reacts analogously with sodium ethoxide.

Scheme 80



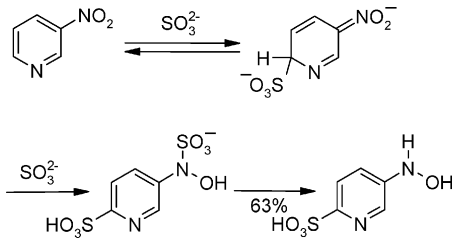
3.7. Sulfur Nucleophiles

There are very few reports on direct replacement of hydrogen in nitroderivatives of aromatic hetero-

cycles with sulfur nucleophiles. Sulfite anion, alkyl- and arylthiolates, and sulfinates are relatively active nucleophiles, but they are also strong reducing agents; thus, often the substitution of hydrogen is accompanied with reduction of the nitro group or reduction is a major process.

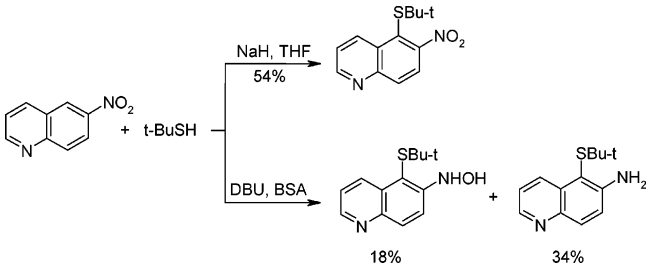
Addition of sulfite ions to 3-nitropyridine is followed by reduction of the nitro group to hydroxylamine (Scheme 81).[248]

Scheme 81



In reaction of *tert*-butylmercaptan with 5- and 6-nitroquinoline, the intermediate σ^H-adduct can be oxidized by another molecule of nitroquinoline to give products of ONSH[249] or when the reaction is carried out in the presence of bis-trimethylsilylacetamide (BSA) an intramolecular redox process took place (Scheme 82).[250]

Scheme 82



3.8. Phosphorus Nucleophiles

Reactions proceeding via addition of phosphorus nucleophiles to electron-deficient arenes and further conversion of σ^H-adducts are reported in very few papers.[251−253]

An interesting reaction belonging to this category that results in formation of phosphorylated benzazepine derivatives was observed when bicyclic nitroarenes (1-nitronaphthalene, 5- and 8-nitroquinoline) were treated with an excess of dimethyl phosphite in the presence of MeONa in MeOH. For example, 5-nitroquinoline converts into phosphorylated pyrido[3,2-*c*]azepine (Scheme 83).[251] According to the proposed mechanism,[253] the nitrosoarene, initially formed via transformations of the σ^H-adduct, undergoes rapid deoxygenation by trivalent phosphorus reagent giving the arylnitrene. Such transformation is well documented as a rapid step in deoxygenation of nitrosoarenes with trialkyl phosphites. Further reactions of the nitrenes proceed in standard ways. Reversible intramolecular cycloaddition to the ring double bond gave azirines which upon addition of methoxide anion give aziridine undergoing subsequent ring expansion to benzazepine derivative.

The ratio of the phosphorylated amino compound and azepine can be affected by kind and concentration of nucleophile. In the presence of an excess of dialkylamine, diazepine derivative can be obtained in high yields.[253]

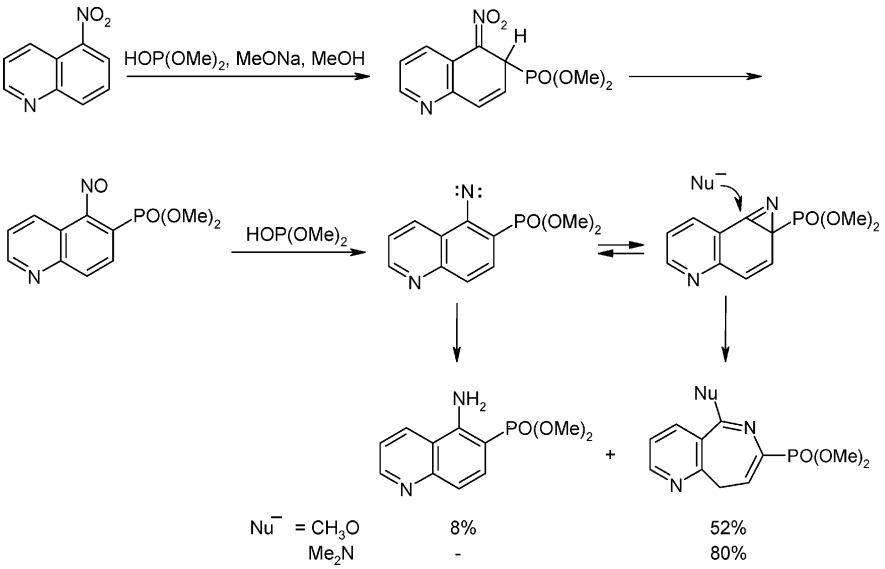
4. Syntheses of Heterocyclic Systems

4.1. Indoles

There are two major pathways of construction of the indole ring via the nucleophilic substitution of hydrogen in nitroarenes: (a) introduction of carbon substituent into *m*-nitroaniline and its derivatives so the amino group nitrogen is in the indole ring and (b) introduction of carbon substituent *ortho* to the nitro group of the nitroarene so the nitro group nitrogen is in the indole ring.

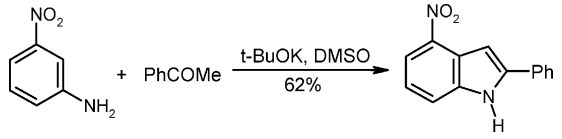
Perhaps the simplest synthesis of 4- and 6-nitroindole derivatives consists of base-promoted oxidative

Scheme 83



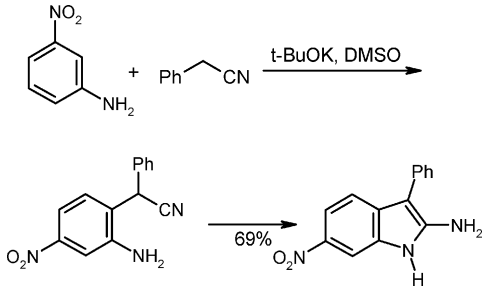
substitution of hydrogen in *m*-nitroanilines by enolate anions of dialkyl, cycloalkyl, and alkyl aryl ketones.[254,255] For example, the reaction of acetophenone and *m*-nitroaniline in the presence of potassium *tert*-butoxide in dimethyl sulfoxide affords 2-phenyl-4-nitroindole (Scheme 84). It appears that the enolates add *ortho* and *para* to the nitro group in the vicinity of the amino group because the σ^H-adducts are additionally stabilized by the interaction of the amino and carbonyl groups. Subsequent oxidation of the σ^H-adducts followed by the intramolecular condensation of the produced *o*-aminobenzyl ketones give nitroindoles.

Scheme 84



Somehow similar is the reaction of *m*-nitroaniline with phenylacetonitrile or some other nitriles. Oxidative nucleophilic substitution of hydrogen *para* to the nitro group and the subsequent addition of the amino to the cyano group gave 2-amino-6-nitro-3-phenylindole (Scheme 85).[256]

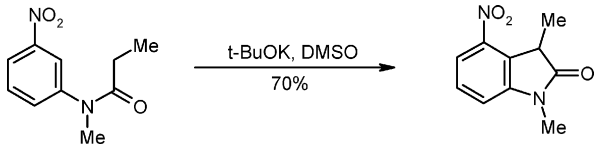
Scheme 85



In both of these reactions intermediate σ^H-adducts are oxidized with oxygen.

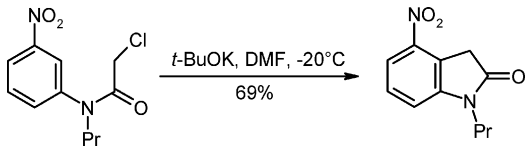
Intramolecular oxidative nucleophilic substitution of hydrogen in *m*-nitro-propionanilides gives access to nitrooxindoles (Scheme 86).[257]

Scheme 86



Direct synthesis of the indole ring system can be accomplished by the intramolecular VNS of the *m*-nitro-substituted chloroacetanilides, giving substituted nitrooxindoles (Scheme 87).[258]

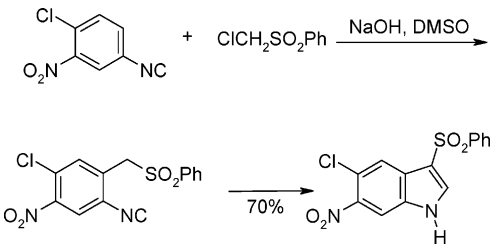
Scheme 87



In both of the reactions shown in the Schemes 86 and 87 the strong preference for substitution of the hydrogen *ortho* to the nitro group was observed giving mainly 4-nitrooxindole derivatives.

The ability of the isocyano group to add nucleophiles was utilized in the direct synthesis of 3-substituted nitroindoles via the VNS reaction of 3-nitrobenzisonitriles, readily available from *m*-nitroanilines, with chloromethyl phenyl sulfone. Under the reaction conditions the initial VNS product cyclizes to nitroindole (Scheme 88).[259]

Scheme 88



Intermolecular reactions of carbanions with nitro group of nitroarenes are uncommon processes,[260−264] whereas such intramolecular reactions readily produce indole ring. Older examples of interaction of *ortho*-alkyl substituents with the nitro group in nitroarenes leading to indole derivatives were reviewed by Preston and Tennant.[265]

o-Nitroarylacetonitriles produced via VNS cyanomethylation of nitroarenes[176,178] are versatile intermediates in the synthesis of indoles via this type of interactions. For instance, Knoevenagel condensation of these nitriles with aliphatic aldehydes gave alkylidenenitriles[266] that undergo base-induced cyclization to indole or quinoline derivatives (Scheme 89).[267]

Allylation of *o*-nitroarylacetonitriles gives products that in the presence of chlorotrimethylsilane and triethylamine cyclize to 3-cyano-1-hydroxy-2-vinylindoles (Scheme 90).[59] Presumably this reaction proceeds via 1,5-elimination of trimethylsilanol from the intermediate trimethylsilyl nitronate, followed by an electrocyclization and hydrogen shift.

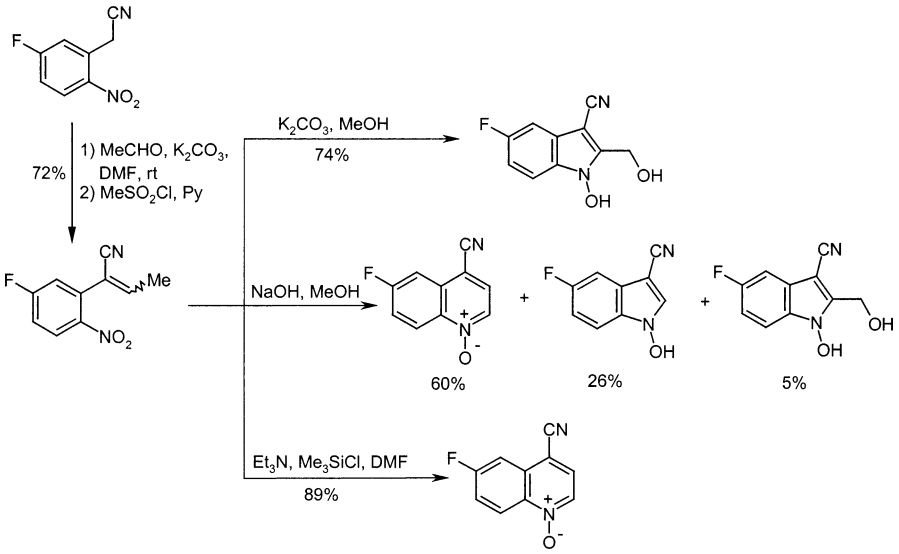
A similar process is postulated for the formation of *N*-hydroxyindole from 2-(5-chloro-2-nitrophenyl)-3-phenylpropionitrile (Scheme 91).[268]

The intermediate vinyl nitroso compound undergoes electrocyclization resulting in formation of nitrone (2*H*-indole *N*-oxide), a tautomer of *N*-hydroxyindole. This supposition was supported by the cyclization reaction of analogous benzhydryl derivative which due to the absence of hydrogen at the created five-membered ring cannot rearrange to *N*-hydroxyindole and forms 2,2-diphenyl-2*H*-indole *N*-oxide derivative in excellent yield (Scheme 92).[268]

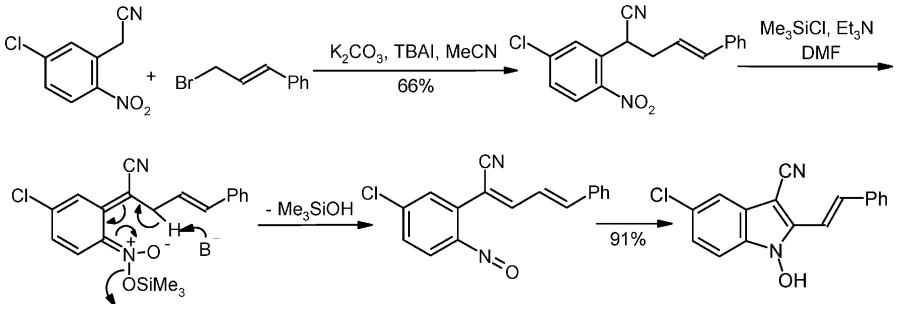
Allyl triphenylphosphonium chloride reacts with 1-nitronaphthalene and 5-nitroquinolines in the presence of tetraisopropyltitanium and DBU to form fused 1-hydroxyindoles, which can deoxygenated to the corresponding indoles (Scheme 93).[269]

o-Nitroaryl derivatives of aldehydes, ketones, esters, and nitriles readily available via VNS or ONSH *ortho* to the nitro group with appropriate carbanions

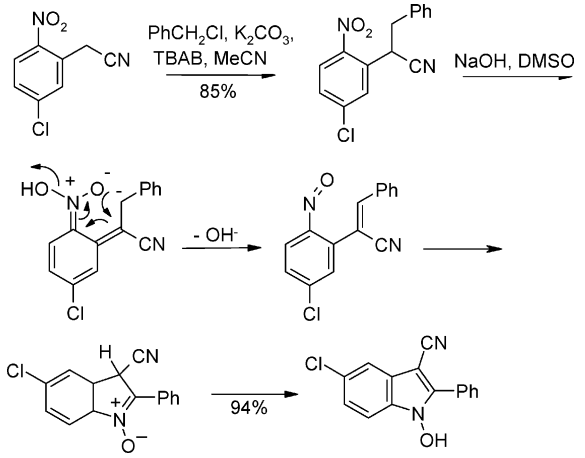
Scheme 89



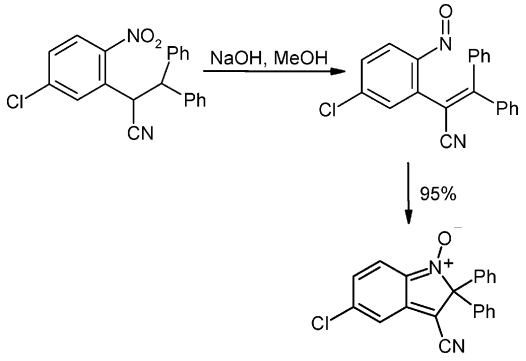
Scheme 90



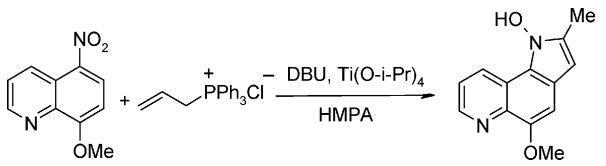
Scheme 91



Scheme 92



Scheme 93

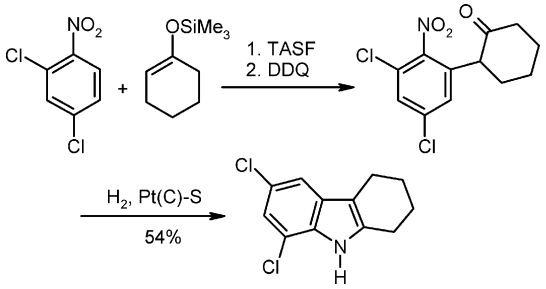


are ideally suited to synthesis of indoles via reduction of the nitro group followed by cyclization. Of particular interest is reduction of the nitro group in *o*-nitrobenzyl ketones because the initially formed *o*-aminobenzyl ketones cyclize directly to indoles.[270,271] This attractive approach to the indole ring construction via reduction of *o*-nitroarylmethyl ketones was of minor practical use because the starting materials were not readily available.[272−276] Thanks to development of new processes of direct introduction of carbonylalkyl substituents into nitroaromatic rings by both VNS and ONSH reactions with enolate anions the required α-(2-nitroaryl)alkyl ketones became easily accessible.

Alternative synthesis of nitrobenzyl ketones via ONSH was developed by RajanBabu. Silyl ethers of enols activated with fluoride anion behave as strong C-nucleophiles and add to nitroarenes in the *ortho*- and *para*-positions to the nitro group giving σ^H-adducts. Oxidation of these σ^H-adducts with DDQ leads to α-(2-nitroaryl)alkyl ketones.[37−39] For example, oxidation of the σ^H-adduct formed in the reaction of substituted nitrobenzenes with 1-trimethylsilyloxycyclohexene activated with tris(dimethylamino)sul-

fonium difluorotrimethylsiliconate (TASF) followed by the oxidation furnishes 2-(2-nitrophenyl)cyclohexanones, which in turn can be reduced to 1,2,3,4-tetrahydrocarbazole derivatives (Scheme 94).[39]

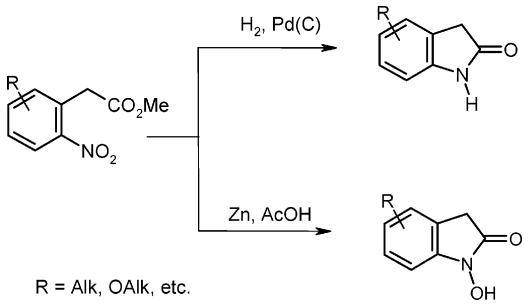
Scheme 94



2-Nitrobenzyl ketones can be also prepared by direct oxidative substitution of hydrogen in the *ortho* position of substituted nitrobenzenes with enolates of methyl ketones.[163,277] Reduction of the produced ketones to indoles was not reported but appears obvious.

One of general methods of synthesis of oxindoles is reductive cyclization of 2-nitrophenylacetic acids and its derivatives.[278,279] Reduction of 2-nitroaryl acetates gives various products depending on the reaction conditions (Scheme 95). Catalytic reduction

Scheme 95

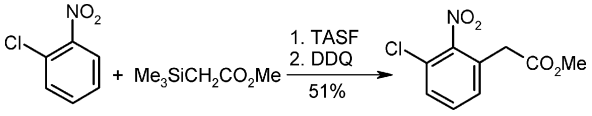


with hydrogen over palladium gives oxindoles,[39,278,279] while the reduction with zinc in acetic acid provides 1-hydroxyoxindoles.[280,281]

In older procedures the required starting materials were prepared by nucleophilic replacement of halogen in *o*-halonitrobenzenes or *o*-nitrophenyltriflates with carbanions of dialkyl malonates followed by hydrolysis and decarboxylation[279] or by condensation of the corresponding 2-nitrotoluenes with diethyl oxalate.[282]

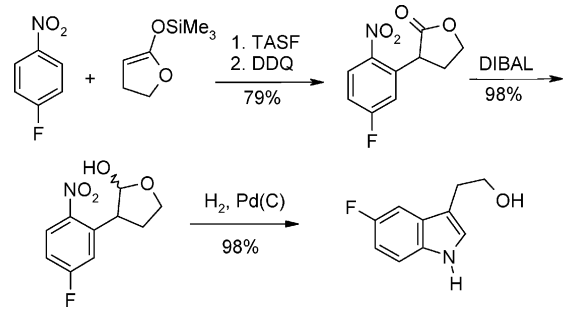
Fluoride ion-induced reaction of methyl trimethylsilyl acetate with nitroarenes gives σ^H-adducts, which after oxidation with DDQ provide (2-nitroaryl)-acetates (Scheme 96).[37−39]

Scheme 96



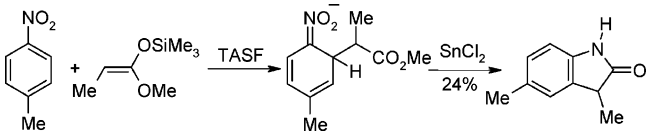
Ketene silyl acetals react with nitroarenes in the presence of fluoride anions similarly to silyl enol ethers and the formed σ^H-adducts of enolates can be oxidized with DDQ or bromine to give nitroarylacetic acid derivatives.[37−39] For example, fluoride ion-induced addition of 2,3-dihydro-5-(trimethylsilyloxy)-furan to *p*-fluoronitrobenzene followed by oxidation with DDQ gives arylbutyrolactone, which subjected to two-step reduction with diisobutylaluminum hydride (DIBAL) followed by catalytic hydrogenation gives 5-fluorotryptophol (Scheme 97).[39]

Scheme 97



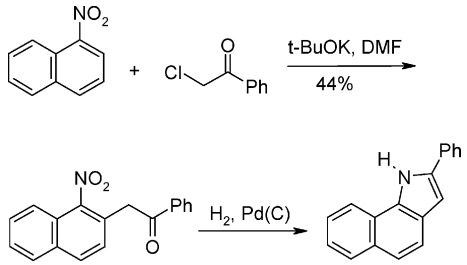
Alternatively, these σ^H-adducts upon treatment with tin(II) chloride can be directly transformed into indolin-2-one derivatives (Scheme 98).[39]

Scheme 98



VNS of hydrogen in nitroarenes with enolate anions of α-chloroalkyl ketones proceeds in moderate yields (Scheme 99);[164] however, the nitroaryl ketones

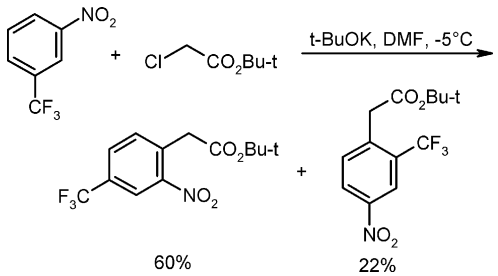
Scheme 99



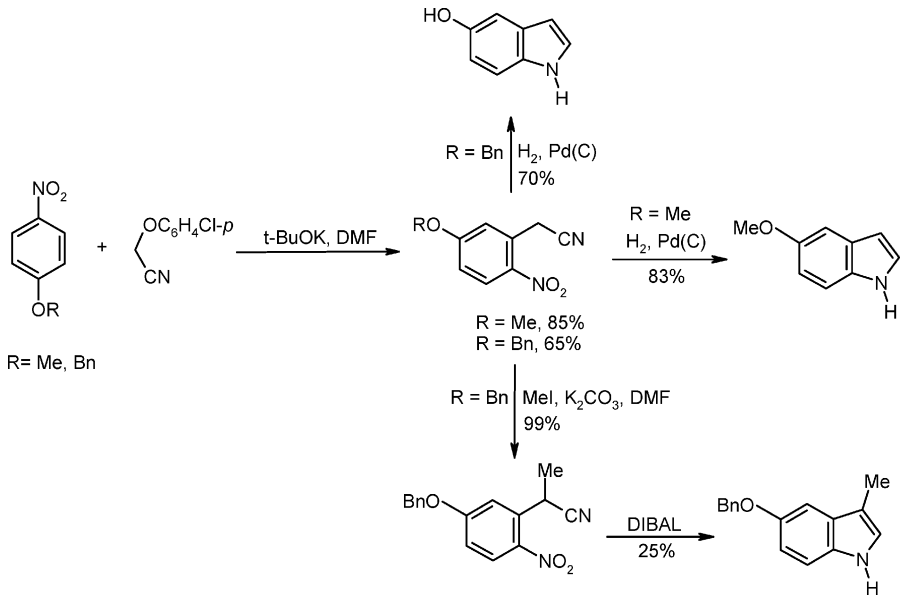
obtained can be transformed into indole derivatives by standard procedures usually in quantitative yields,[272−276,283] thus making the whole process preparatively useful.

VNS of hydrogen provides access to esters of 2-nitroarylacetic acid with a variety of substituents by the direct reaction of nitroarenes with alkyl chloroacetates (Scheme 100).[171]

Scheme 100



Scheme 101

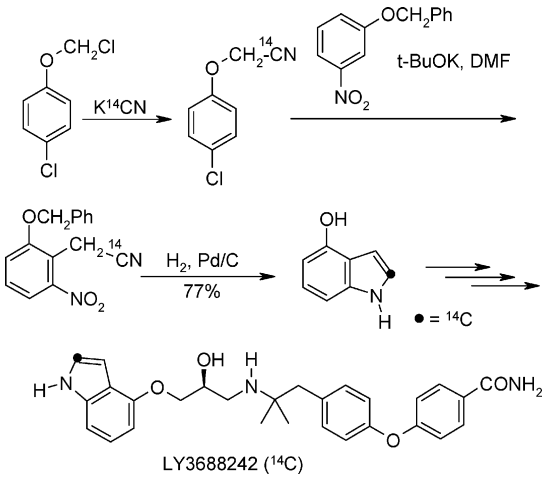


One of the most valuable methods for the synthesis of indole derivatives consists of the reductive cyclization of (*o*-nitroaryl)acetonitriles.[278,284] The reaction known for many years has been however of minor practical use because the required nitriles were not readily available. Thanks to the possibility of direct introduction of cyanomethyl group into a nitroarene moiety by VNS of hydrogen with chloroacetonitrile,[176] aryloxyacetonitriles,[178] and arylthioacetonitriles,[177,285] this process becomes an attractive method for the synthesis of substituted indoles starting from easily available nitroarenes.[178,184,286,287] Introduction of cyanomethyl group into nitroarenes via ONSH[163,288] is also possible but perhaps less general and of minor practical use.

The *o*-nitroarylacetonitriles readily available by this way are widely used in further reductive transformations into indoles, as exemplified by the synthesis of isomeric 4-, 5-, 6-, and 7-hydroxy- and methoxyindoles from isomeric nitrophenols. Since in basic media nitrophenols exist in the form of the corresponding phenolate anions and are not susceptible to nucleophilic attack, the phenolic hydroxy group should be protected before the VNS reaction. Using various alkyl protecting groups and reduction procedures one can obtain a variety of alkoxy- or hydroxyindoles from the cyanomethylated nitrophenols.[178,289,290] For example, VNS of hydrogen in 4-nitroanisole in the reaction with the carbanion of (4-chlorophenoxy)acetonitrile proceeds in good yield and the catalytic hydrogenation of the obtained 5-methoxy-2-nitrophenylacetonitrile over palladium gives 5-methoxyindole.[178] When benzyl 4-nitrophenyl ether was used as the starting material the catalytic reduction of the formed 5-benzyloxy-2-nitroarylacetonitrile leads to 5-hydroxyindole,[178] while benzyloxyindole can be obtained when diisobutylaluminum hydride (DIBAL) was used for simultaneous reduction of the cyano and nitro groups (Scheme 101).[287]

This protocol was recently applied to the synthesis of 4-hydroxyindole labeled with ^{14}C at the 2-position, the key intermediate for the synthesis of ^{14}C-labeled

Scheme 102



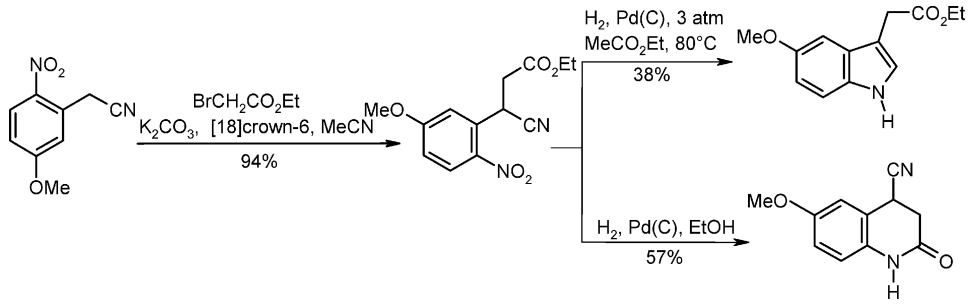
β_3 adrenergic agonist LY368842 (Scheme 102).[291] The required chlorophenoxyacetonitrile was prepared from commercially available 4-chlorophenoxymethyl chloride and $K^{14}CN$.

An additional value of the synthesis of indoles via the VNS cyanomethylation is connected with the possibility of alkylation of the nitroarylacetonitriles with alkyl halides[178,266] or alcohols,[286,292] leading to precursors of 3-substituted indoles.[178,286,292] For example, alkylation of *o*-nitroarylacetonitrile with ethyl bromoacetate gave ethyl 3-(*o*-nitroaryl)-3-cyanopropionate, which upon reduction can cyclize in two directions, giving indole or quinoline derivatives (Scheme 103).[178]

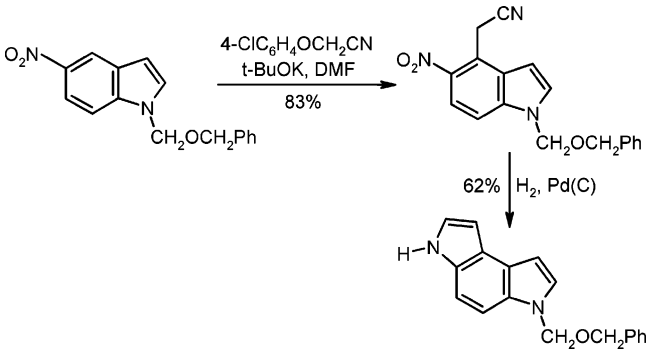
The VNS cyanomethylation of *N*-protected 5-nitroindole[183] followed by reduction of the obtained 4-(cyanomethyl)-5-nitroindole was used for preparation of pyrrolo[3,2-*e*]indole derivative (Scheme 104),[184] a parent heterocyclic fragment of an antitumor antibiotic CC-1065.[293]

Reduction of the nitro group in *o*-nitroarylmethyl ketones, esters, and nitriles results in immediate cyclization to indole derivatives. Attractive possibilities are provided also by reduction of *o*-nitroarylmethyl

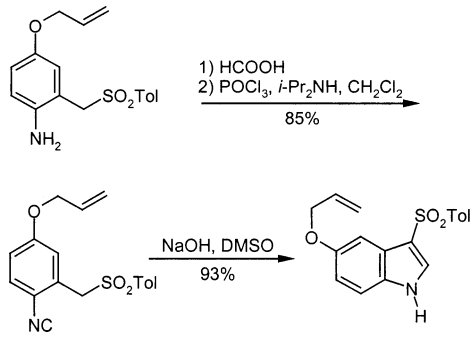
Scheme 103



Scheme 104



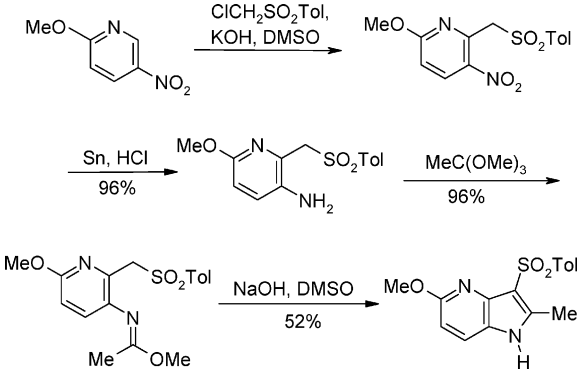
Scheme 106



aryl sulfones readily obtained via VNS in nitroarenes with chloromethyl aryl sulfones.[75]

Reduction of *o*-nitrobenzyl sulfones with tin in a hydrochloric acid−methanol mixture furnishes the corresponding amines, which can be transformed into indole derivatives in a variety of ways. Thus, the condensation of the amino sulfone with methyl orthoacetate gives an imidate, which cyclizes under basic conditions to give 3-sulfonylindole (Scheme 105).[294]

Scheme 105



Alternatively, 2-aminobenzyl sulfone can be converted by a standard procedure (formylation−dehydration) into 2-isocyanobenzyl sulfone, which also cyclizes to 3-sulfonylindole upon treatment with a base (Scheme 106).[295]

Condensation of *o*-aminobenzyl sulfones with aromatic or heteroaromatic aldehydes leads to the imines, which in the presence of NaOH in DMSO cyclize to 2-aryl-substituted indoles via an intermediate, 2,3-dihydroindole, that undergoes further β-elimination of arenesulfinic acid (Scheme 107).[296]

1,8-Diazabicyclo[5.4.0]undec-8-ene (DBU) in reaction with 1,3,5-trinitrobenzene and methyl 3,5-dinitrobenzoate forms condensed pyrimidine derivatives. In the first step of this transformation DBU acts as C-nucleophile producing intermediate amidine, which via intramolecular reaction replaces the nitro group to give the condensed indole derivative (Scheme 108).[297]

Intramolecular VNS reaction in pyridinium salt derived from 2-chloroquinoxaline derivative proceeds with an elimination of toluenesulfinic acid furnishing indolizino[2,3-*b*]quinoxaline (Scheme 109).[298]

4.2. 2*H*-Isoindoles

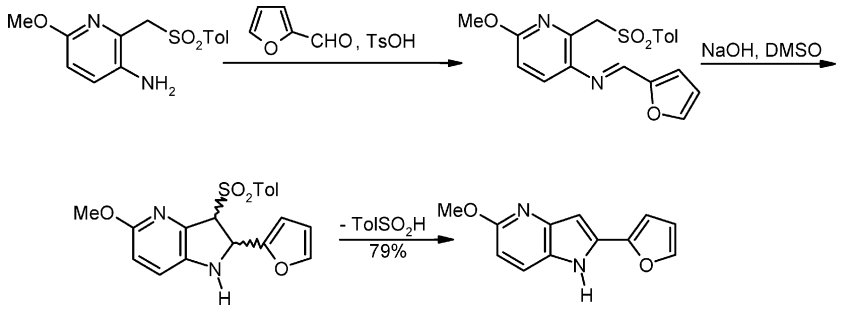
Intramolecular ONSH with carbanions of *m*-nitroarylamidonitriles gives direct access to isoindolin-1-ones (Scheme 110).[299] In this process the intermediate σ^H-adducts are oxidized apparently by oxygen.

A general method of synthesis of pyrrole derivatives via reaction of carbanions of alkyl isocyanoacetates or tosylmethylisocyanide (TosMIC) with activated alkenes developed by van Leusen[300] has been adopted to prepare 3,4-fused pyrroles (isoindoles) from nitroarenes. The carbanion of ethyl isocyanoacetate generated in the presence of DBU in THF reacts with some nitroarenes, such as mono- and dinitronaphthalenes,[301−303] 5-nitroisoquinoline,[303] 2-nitrofuran,[303] 1-nitroacenaphthene,[304,305] 9-nitrophenanthrene,[301,304,306] 9-nitrophenanthroline,[301,304,307] 3-nitrobenzothiophene,[301] 4-nitrobenzo-2,1,3-thiadiazole,[302,304,308,309] and 4-nitrobenzo-2,1,3-selenadiazole,[309] to give condensed pyrroles (Scheme 111).[301−303]

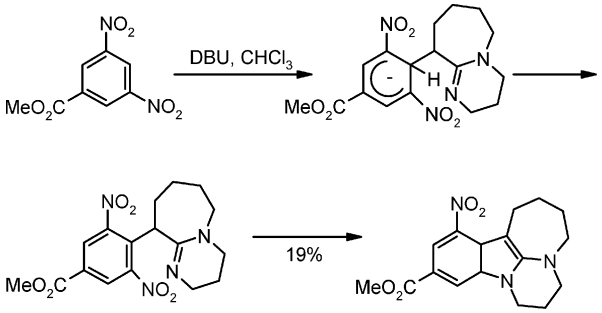
These reactions proceed undoubtedly via σ^H-adducts of the corresponding carbanion to the nitroaromatic rings in position *ortho* to the nitro group, which then undergo multistep transformations to the final products and thus can be considered as nucleophilic *cine*-substitution of hydrogen.

Isoindoles can be efficiently produced via an air oxidation of carbanions of benzothiazine 2,2-dioxides

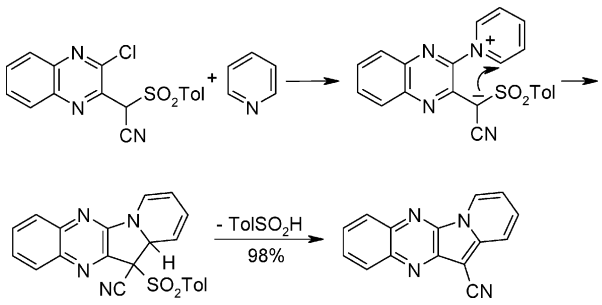
Scheme 107



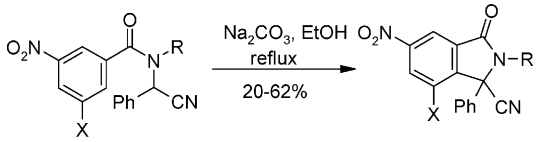
Scheme 108



Scheme 109

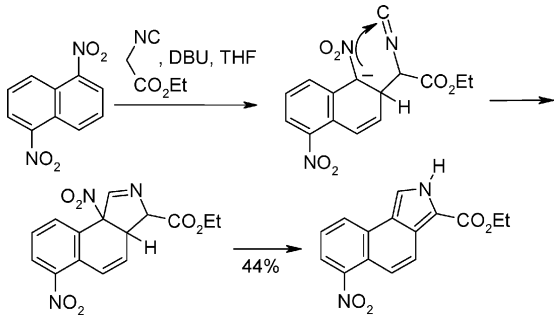


Scheme 110



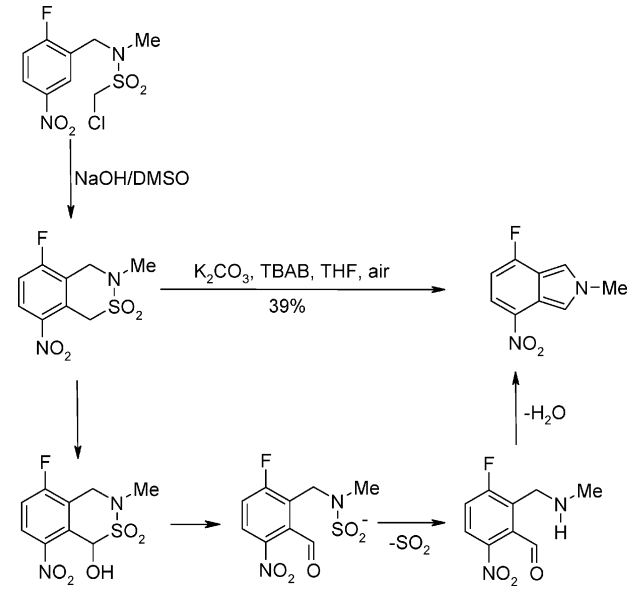
X = H, NO_2
R = Me, Ph, CH_2Ph

Scheme 111



readily available by intramolecular VNS in *m*-nitrobenzyl sulfonamides (Scheme 112).[310] This reaction presumably proceeds via intermediate aldehyde, which undergoes cyclization with elimination of water.

Scheme 112



4.3. 1*H*-Indazoles

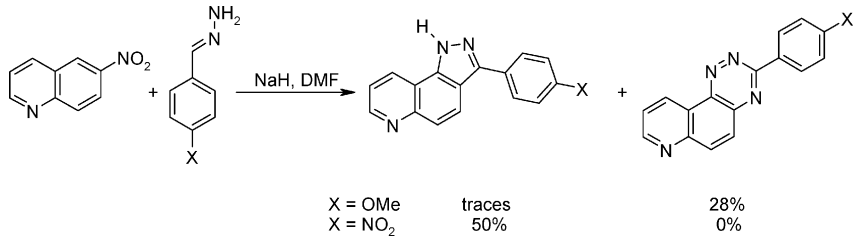
Highly electrophilic nitroarenes react with anions of hydrazones of arylaldehydes to form 3-arylindazole derivatives.[311,312] The reaction course strongly depends on the reaction conditions as well as on the structure of the reacting species; in particular, the electronic effects of substituents present in the *para* position of the hydrazone are decisive. Thus, anions of hydrazones of aromatic aldehydes containing an electron-donating substituent (e.g., methoxy group) form 1,2,4-triazine ring, while electron-withdrawing groups (e.g., nitro) favor formation of condensed pyrazole as exemplified in the reaction with 6-nitroquinoline (Scheme 113).[311,312]

Formation of intermediate σ^H-adduct is involved in oxidative cyclization of the 2-acetylquinoxaline phenylhydrazone (Scheme 114).[313] The reaction proceeds satisfactorily at elevated temperatures in the presence of various oxidants, such as nitrobenzene, elemental sulfur, DDQ, etc.

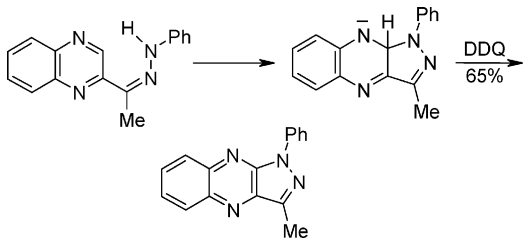
4.4. Benzimidazoles

Cyclic five-, six-, and seven-membered *N*-(3-nitrophenyl)guanidines enter intramolecular oxidative substitution of hydrogen with nitrogen nucleophiles.[314] The orientation of the intramolecular nucleophilic substitution of hydrogen can be controlled by the reaction conditions, as shown in the reaction of 2-[benzyl(3-nitrophenyl)amino]-1,2,3,4-tetrahydro-

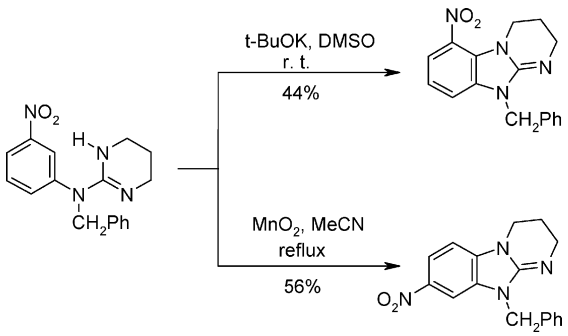
Scheme 113



Scheme 114



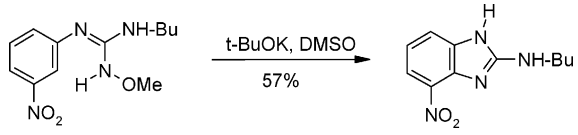
Scheme 115



pyrimidine (Scheme 115). When the reaction is carried out in the presence of t-BuOK in DMSO, substitution of hydrogen *ortho* to the nitro group takes place, while in the presence of manganese(IV) dioxide in boiling acetonitrile, replacement of hydrogen *para* to the nitro group is observed.[314]

Intramolecular VNS in N^1-(3-nitrophenyl)-N^2-alkoxyguanidines results in formation of nitrobenzimidazoles.[315] The reaction proceeds predominantly in the *ortho* position to the nitro group (Scheme 116).

Scheme 116

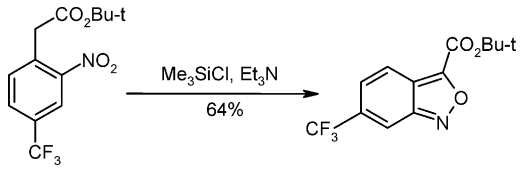


4.5. 2,1-Benzisoxazoles

Reactions of phenylacetonitrile with *para*-substituted nitrobenzenes in the presence of sodium hydroxide in protic systems such as aqueous methanol results in formation of benzisoxazoles obviously via σ^H-adduct, which undergoes elimination of water to produce nitroso compound and subsequent cyclization with elimination of hydrogen cyanide (Scheme 1, eq 1b).[11,53]

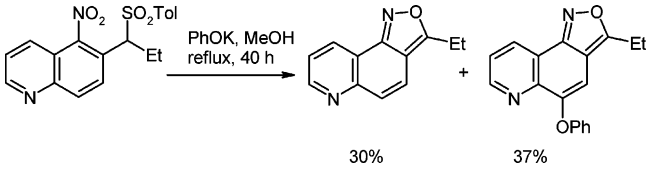
2,1-Benzisoxazoles are also formed via dehydration of the *o*-nitroarylacetic esters, nitriles, and *o*-nitrobenzyl sulfones, products of the VNS reaction in nitroarenes, upon treatment with chlorotrimethylsilane in the presence of triethylamine (Scheme 117).[61] This is perhaps the simplest, most versatile, and efficient method of synthesis of this ring system.

Scheme 117



Formation of 2,1-benzisoxazoles was observed also when the VNS products obtained from bicyclic nitroarenes and heteroarenes were subjected to reaction with phenolate[316] and thiolate anions[316,317] or even with some carbanions.[317] For example, when a sulfone obtained from 5-nitroquinoline was treated with potassium phenoxide, a mixture of two condensed benzisoxazoles was formed (Scheme 118).[316]

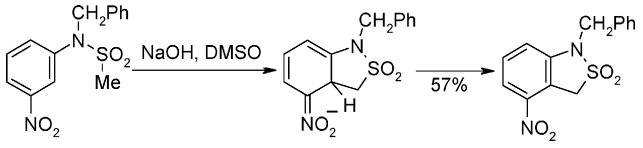
Scheme 118



4.6. 2,1-Benzisothiazoline 2,2-Dioxides

Intramolecular addition of carbanions generated from *N*-alkanesulfonyl-*m*-nitroanilines proceeds predominantly in the *ortho* position to the nitro group to form σ^H-adducts, which are converted into 2,1-benzisothiazoline 2,2-dioxides (benzosultams) via the oxidation apparently by oxygen (Scheme 119).[318−320]

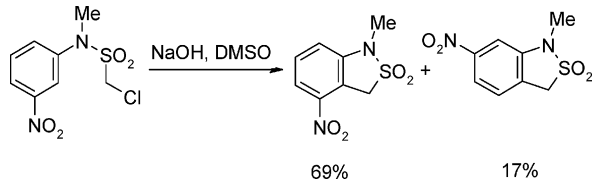
Scheme 119



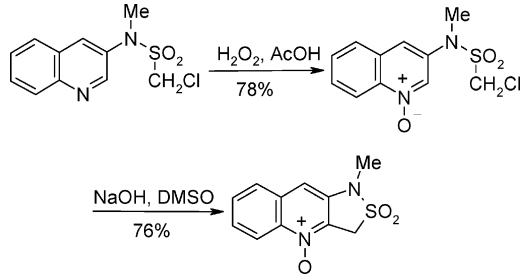
Similarly to mentioned earlier *m*-nitro chloroacetanilides react *N*-alkyl-*N*-chloromethane-sulfonyl-3-nitroanilines, which upon treatment with strong base enter intramolecular VNS reaction to give a mixture of 4- and 6-nitrobenzosultams (Scheme 120).[321,322]

Pyridine and quinoline rings activated via *N*-oxidation undergo the VNS of hydrogen in the reaction with chloromethyl aryl sulfones.[181,201] This reaction proceeds readily also as an intramolecular process. For example, chloromethanesulfonamide of 3-aminoquinoline cyclizes to isothiazolo[4,3-*b*]quinoline 2,2,4-trioxide (Scheme 121).[323]

Scheme 120

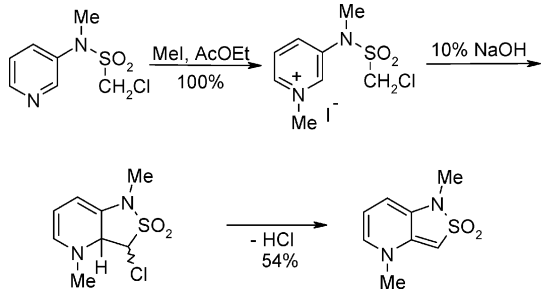


Scheme 121



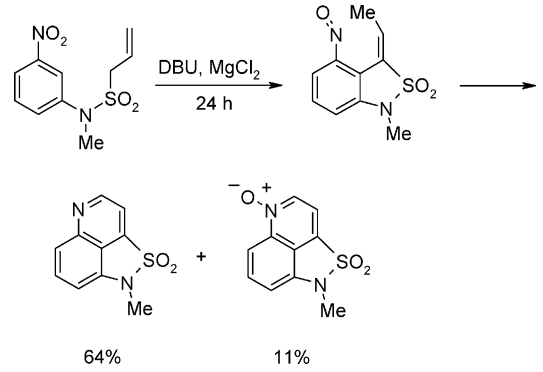
Highly electron-deficient pyridinium and quinolinium salts readily enter intramolecular VNS of hydrogen: 3-(*N*-methyl)pyridinium chloromethanesulfonamide in the presence of 10% aqueous NaOH reacts according to the intramolecular VNS pathway giving 1,4-dihydroisothiazolo[4,3-*b*]pyridine 2,2-dioxide (Scheme 122).[323]

Scheme 122



N-(Allylsulfonyl)-3-nitroaniline in the presence of a mild base and Lewis acid enters multistep transformation into 2,2-dioxoisothiazolo[5,4,3-*de*]quinoline (Scheme 123). Initially formed σ^H-adduct is converted

Scheme 123



into nitroso compound, which then undergoes cyclization to the pyridine ring.[66]

Similar cyclization proceeds upon treatment of *N*-benzylsulfonyl-3-nitroaniline with DBU and *tert*-butyldimethylchlorosilane. The intermediate σ^H-adduct is converted into nitroso compound, which undergoes further silylation under the reaction conditions to form 4-silyloxyimino-1,4-dihydro-2,1-benzisothiazole 2,2-dioxide.[324] The quinoidal compound being an analogue of aza-*ortho*-xylylene[325] upon UV irradiation undergoes photochemical 6π-electrocyclization and subsequently elimination of trialkylsilanol to give dioxoisothiazolo[5,4,3-*kl*]acridine (Scheme 124).[324]

4.7. Quinolines and Other Condensed Pyridines

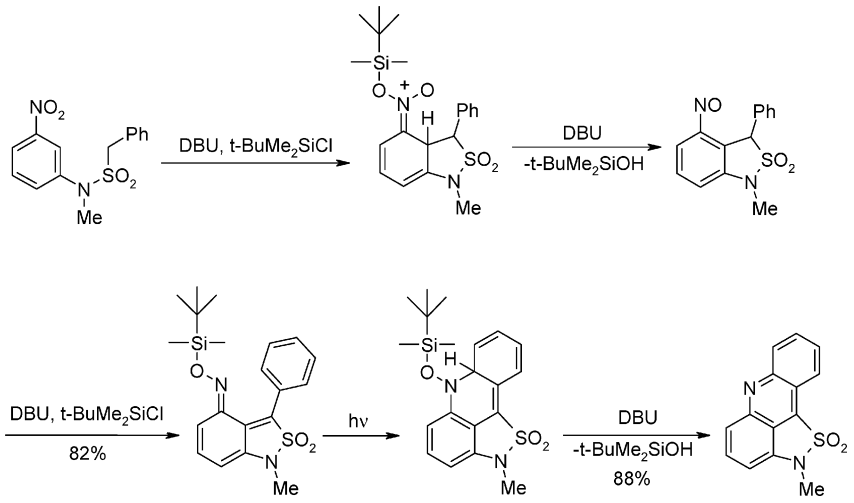
Introduction of substituents into the *ortho* positions of nitroarenes via nucleophilic substitution of hydrogen provides new attractive possibilities for synthesis of quinolines. Construction of the quinoline ring containing a nitrogen atom originating from the nitro group can proceed as direct condensation of the latter with the side chain introduced by nucleophilic substitution of hydrogen or via its initial reduction to the amino group followed by condensation with the functional group in the side chain. It is also possible to form the quinoline ring in a one-pot reaction of carbanions with nitroarenes, the process embracing substitution of hydrogen and further transformations. Preston and Tennant reviewed older examples of the synthesis of quinolines from *ortho*-functionalized nitroarenes.[265]

Recently it was reported that some allylic carbanions react with nitroarenes in the presence of silylating agents or Lewis acids to form substituted quinoline derivatives.[65] This reaction proceeds satisfactorily when relatively active nitroarenes, such as 4-chloronitrobenzene, 1-nitronaphthalene, 2-nitrothiophene, nitropyridines, 5- and 8-nitroquinolines, etc., are treated with carbanions of cinnamyl phenyl sulfone (Scheme 125),[58,65] cinnamonitrile,[65] and dimethyl cinnamylphosphonate.[65] These reactions proceed apparently via conversion of the initially formed σ^H-adducts into the nitroso compounds followed with cyclization and elimination of water.[58] In the formed sulfonylquinoline the arenesulfonyl group can be easily replaced by a variety of nucleophiles (thiolates, azide, cyanide, and methyl cyanoacetate anions) or it can be removed by reduction with sodium borohydride, giving access to a variety of functionalized quinoline derivatives.[65]

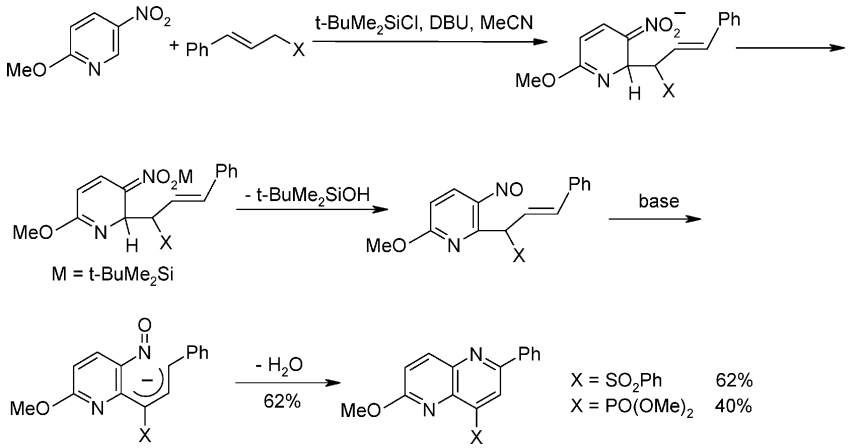
o-Nitrobenzyl sulfones readily available via the VNS reaction react with diethyl maleate or fumarate to form dimethylquinoline-2,3-dicarboxylate *N*-oxides. This multistep reaction consists of base-catalyzed Michael addition of the sulfone carbanion followed by elimination of benzenesulfinate and finally intramolecular attack of the intermediate allylic carbanion on the nitro group with elimination of water. For example, reaction of nitrothienyl phenyl sulfone with dimethyl fumarate gave to diethyl thienopyridinedicarboxylate-*N*-oxide (Scheme 126).[326]

It was shown that alkylidene nitriles, products of the Knoevenagel condensation of *o*-nitroarylacetonitriles and aliphatic aldehydes,[266] cyclize to 1-hydroxyindole derivatives and quinoline *N*-oxides upon treatment with basic agents (Scheme 89).[267,327] The cyclization pathway of these alkylidene nitriles strongly depends on the reaction conditions. For example, the nitrile in methanolic NaOH solution

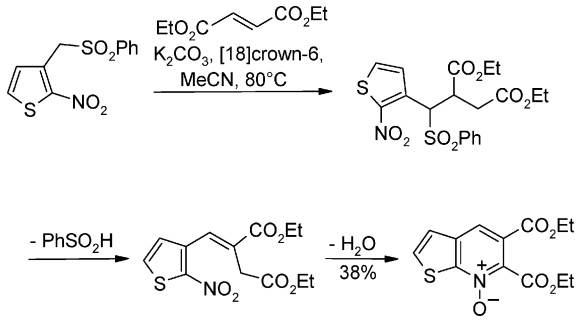
Scheme 124



Scheme 125



Scheme 126

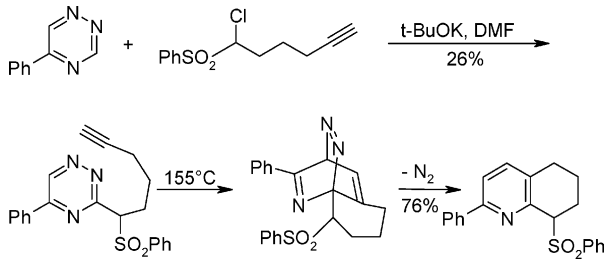


converts into a mixture of *N*-hydroxyindole, *N*-hydroxy-2-(hydroxymethyl)indole, and quinoline-*N*-oxide, whereas in the presence of K_2CO_3 in methanol, the major product is indole,[267] and in the presence of trimethylamine and chlorotrimethylsilane, quinoline *N*-oxide is formed selectively.

VNS of hydrogen in 1,2,4-triazines combined with intramolecular Diels−Alder reaction/*retro*-cycloaddition was used for the synthesis of 5,6,7,8-tetrahydroquinoline derivatives (Scheme 127).[199]

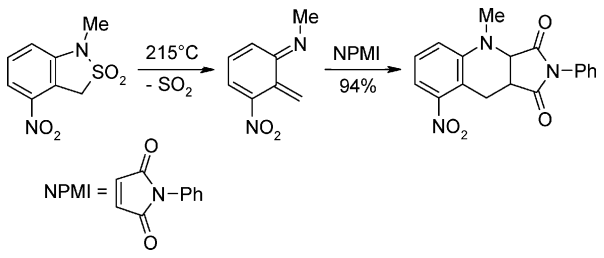
Interesting possibilities of synthesis of condensed quinoline systems are offered by [4+2] cycloaddition reactions of short-lived aza-*ortho*-xylylenes[325] generated by thermal (>180 °C) extrusion of sulfur dioxide from benzosultams, which are readily accessible via

Scheme 127

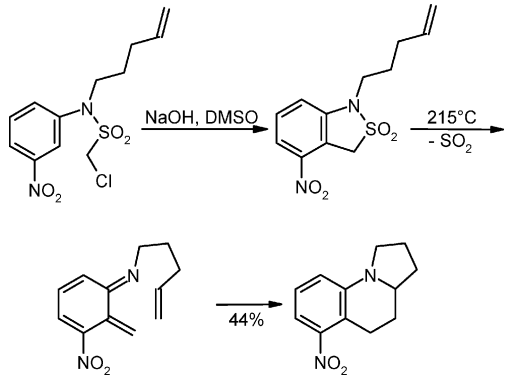


intramolecular, oxidative (Scheme 119),[318,319] or vicarious (Scheme 120)[322] substitution of hydrogen in 3-nitro-*N*-(methane or chloromethanesulfonyl)anilines. Aza-*ortho*-xylylenes can be trapped with a dienophile, e.g., *N*-phenylmaleimide (NPMI), to form condensed 1,2,3,4-tetrahydroquinoline derivatives (Scheme 128).[213,325,328,329]

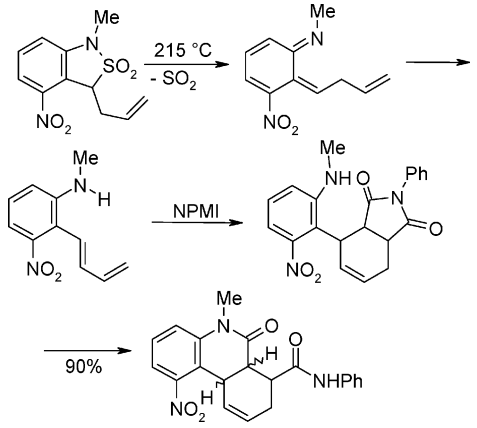
Scheme 128



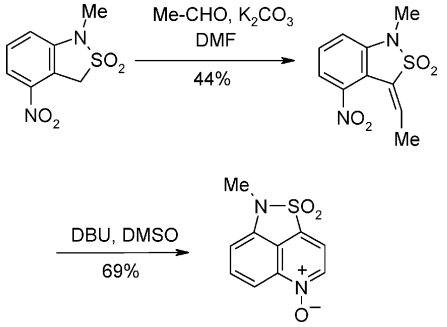
Scheme 129



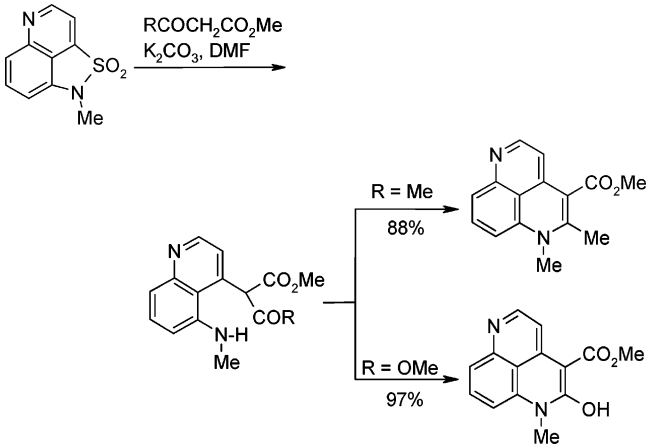
Scheme 130



Scheme 131

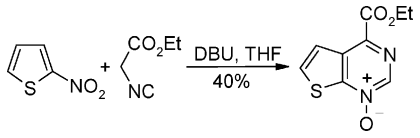


Scheme 132

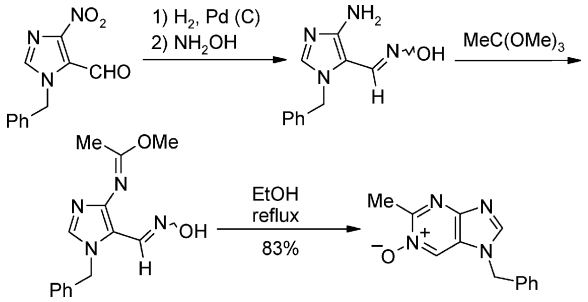


Intramolecular VNS in *N*-pentenyl- and *N*-hexenyl-*N*-chloromethanesulfon(*m*-nitro)anilides provides benzosultams that undergo thermal extrusion of SO_2 leading to aza-*ortho*-xylylenes suitable for intramolecular [4+2] cycloaddition leading to 1,2,3,4-tetrahydroquinoline derivatives (Scheme 129). [329]

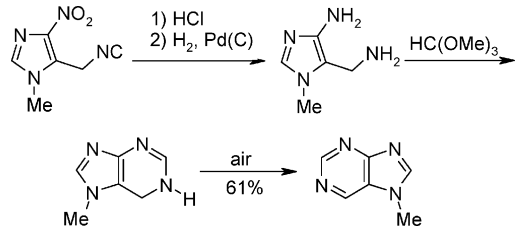
Scheme 133



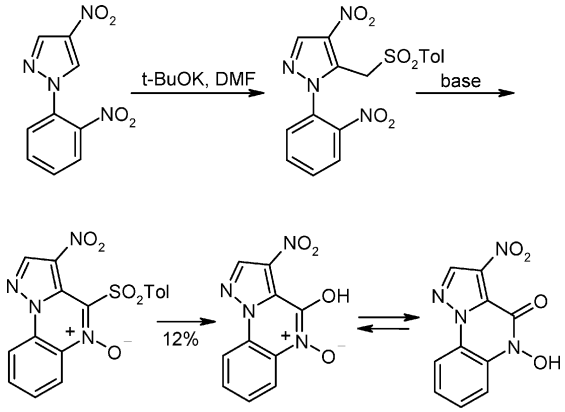
Scheme 134



Scheme 135



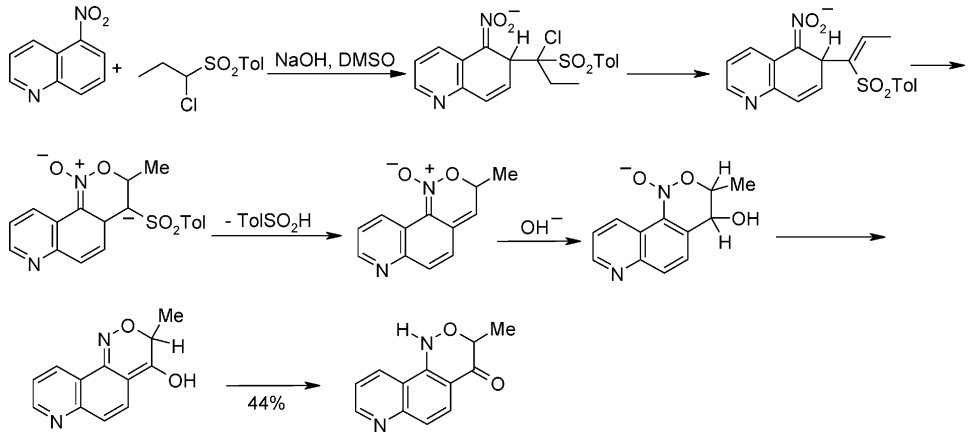
Scheme 136



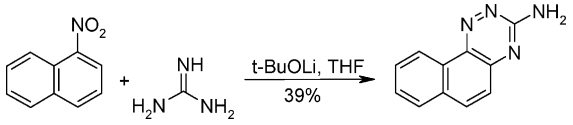
Aza-*ortho*-xylylenes generated from 3-alkylbenzosultams do not enter [4+2] cycloaddition but undergo a [1,5] sigmatropic hydrogen shift leading to 2-vinylaniline derivatives.[330−332] A domino reaction consisting of a series of pericyclic processes including cheletropic extrusion of SO_2, [1,5] sigmatropic hydrogen shift, and [4+2] cycloaddition takes place in thermally initiated transformation of 1-allyl-4-nitrobenzosultams.[330,333] Thus, 1-methyl-3-allyl derivative of benzosultam undergoes thermolysis to 1-arylbuta-1,3-diene, which can be trapped by *N*-phenylmaleimide to form phenanthrolinone (Scheme 130).[333]

Knoevenagel condensation of benzosultams with acetaldehyde gives the corresponding ethylidene derivative that in the presence of diazabicycloundecene (DBU) undergoes cyclization to the tricyclic sultam (Scheme 131).[66,334] The reaction proceeds

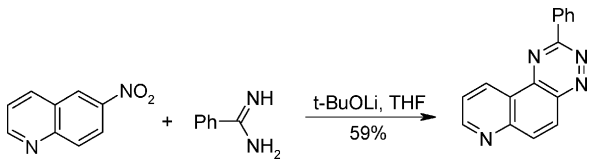
Scheme 137



Scheme 138



Scheme 139



apparently via intramolecular addition of the allylic carbanion to the nitro group.

The sulfonyl group in this tricyclic sulfonamide can be easily substituted by nucleophiles.[324,335] For example, reaction of the sultam with methyl acetoacetate anion gives 1*H*-benzo[*i*,*j*][1,5]naphthyridine (Scheme 132). In a similar reaction with dimethyl malonate, the corresponding hydroxy derivative is formed.[335]

4.8. Condensed Pyrimidines

It was mentioned earlier (Scheme 111) that ethyl isocyanoacetate in the base-induced reaction with some nitroarenes produces isoindole derivatives.[301−304,306] Another reaction course was observed when ethyl isocyanoacetate was reacted with 2-nitrothiophene,[309] 5-nitro-2,1,3-benzothiadiazole,[309,336] and 5-nitro-2,1,3-benzoselenadiazole.[309,336] Instead of a *cine*-substitution of the nitro group analogous to that shown in the Scheme 111, intramolecular reaction of the entering nucleophile with the nitro group takes place, resulting in formation of condensed pyrimidine *N*-oxide (Scheme 133).

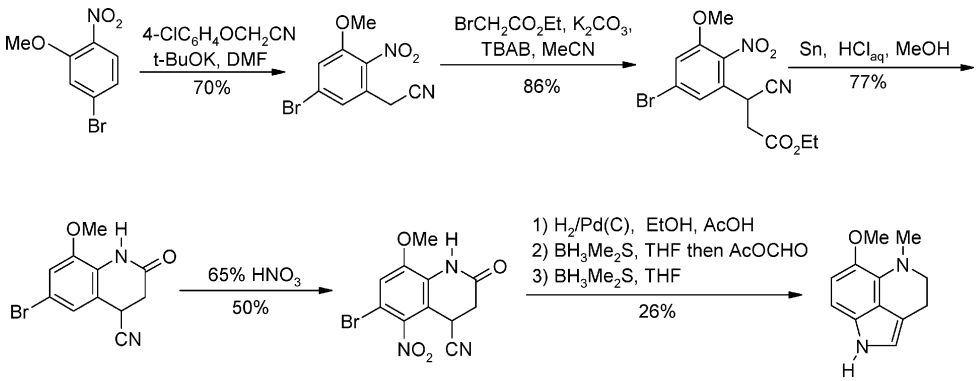
From the reported data[309,336] it appears that the reaction course to give pyrrole or pyrimidine ring depends on the structure of nitroarene and used base. A speculative mechanism of these transformations has been proposed.[309,336]

Pyrimidine rings are readily constructed from *o*-nitro- and *o*-aminoarylaldehydes. These important intermediates can be produced via nucleophilic substitution of hydrogen. Thus, the VNS reaction with chloroform can be considered as a nucleophilic formylation due to facile hydrolysis of the introduced dichloromethyl group.[71,337] Aromatic *o*-nitroarylaldehydes readily accessible in this way were used for efficient synthesis of condensed pyrimidines. For example, reduction of the nitro group in 2-nitrobenzaldehyde oximes leads to the corresponding anilines, which can be transformed into a variety of condensed heterocycles by several methods.[159,160,338−340]

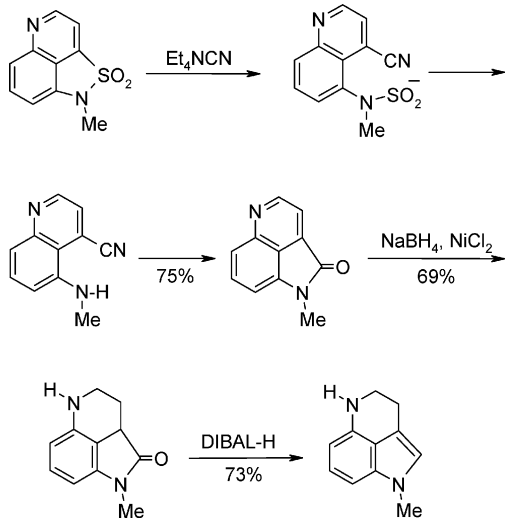
Imidates obtained in reaction of these amines with ortho esters undergo electrocyclization followed by elimination of alcohol moiety, furnishing condensed pyrimidine mono-*N*-oxides.[160,339,340] This method enables synthesis of a variety of condensed heterocyclic systems, such as, thieno[3,2-*d*]pyrimidine-3*N*-oxide, benzo[*h*]quinazolin-3*N*-oxide, pyrido[3,2-*h*]quinazolin-3*N*-oxide, and others.

This approach to condensed pyrimidines is of particular interest for the synthesis of purine derivatives starting from 4-nitroimidazole-5-carbaldehydes

Scheme 140



Scheme 141



readily available from 1-substituted-4-nitroimidazoles via VNS dichloromethylation followed by hydrolysis.[71,159,160,337,338,340] This is an example of purine synthesis in which the six-membered ring is constructed over the existing five-membered imidazole ring, a strategy not commonly used in the synthesis of purines (Scheme 134).[339]

(*o*-Nitroaryl)methylisocyanides obtained via the VNS in nitroarenes with phenylthiomethylisonitrile carbanion (Scheme 48)[187] are also useful starting materials for the synthesis of condensed pyrimidine derivatives.[188] Hydrolysis of the *o*-nitroarylisonitrile to amine followed by catalytic reduction of the nitro group leads to (*o*-aminoaryl)methylamines, which condensed with ortho ester form dihydropurine, subsequently oxidized by air to 7-methyl-7*H*-purine (Scheme 135).[340]

4.9. Condensed Pyrazines

The VNS reaction of 1-(*o*-nitrophenyl)-4-nitropyrazole with chloromethyl tolyl sulfone provides 5-tosylmethyl derivative which under the reaction conditions reacts with the nitro group present in the benzene ring to form 3-nitro-5-oxy-pyrazolo[1,5-*a*]-quinoxalin-4-ol, existing in tautomeric equilibrium with 5-hydroxy-3-nitro-5*H*-pyrazolo[1,5-*a*]quinoxalin-4-one (Scheme 136).[207]

4.10. Condensed 1,2-Oxazines

Condensed 1,2-oxazin-4-ones were formed in the reactions of 1-nitronaphthalene[341] and 5-nitroquinoline[185] with carbanion of α-chloropropyl tolyl sulfone. Apparently the intermediate σ^H-adduct, due to steric hindrance, does not enter *β*-elimination of HCl but undergoes a complicated multistep transformation leading to the final product (Scheme 137).[185]

4.11. Condensed 1,2-Thiazines

Intramolecular VNS in *N*-chloromethanesulfonamides derived from 3-nitrobenzylamines leads to nitro derivatives tetrahydro-1*H*-benzo[*d*][1,2]thiazine 2,2-dioxides (Scheme 112).[322]

4.12. Condensed 1,2,4-Triazines

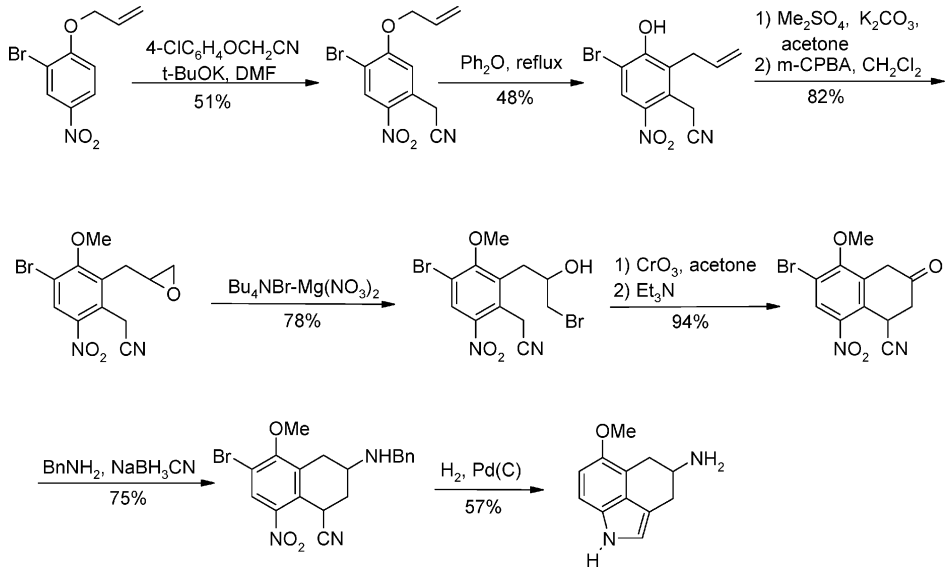
Synthesis of condensed benzotriazines from hydrazones of aromatic aldehydes was shown in the Scheme 119.[311,312] Another approach consists of a cyclocondensation of nitronaphthalenes and nitroquinolines with guanidines.[342] Thus, the reaction of nitronaphthalene with guanidine base in the presence of lithium *tert*-butoxide in refluxing THF leads to 3-aminonaphtho[2,1-*e*][1,2,4]triazine (Scheme 138).[342]

In a similar reaction, amidines form condensed 3-alkyl- or aryl-substituted triazines, as, for example, from 6-nitroquinoline and benzamidine (Scheme 139).[342]

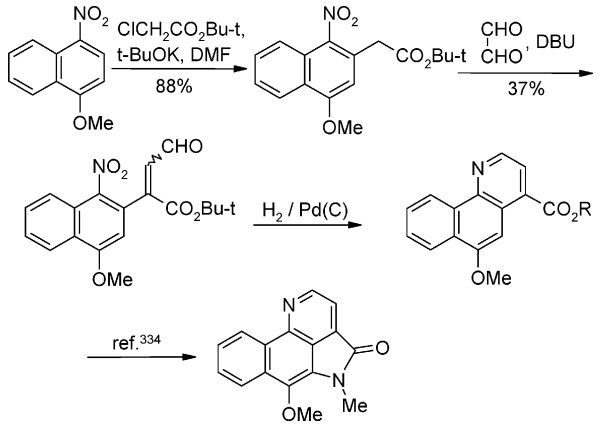
5. Synthesis of Natural Products

Indole and quinoline ring systems are frequently present in natural products and biologically active compounds. Facile synthesis of such heterocycles via nucleophilic substitution of hydrogen presented above offers a valuable tool for synthesis of these com-

Scheme 142



Scheme 143



pounds. However, to date there are not many examples of the application of the VNS or ONSH reactions in the synthesis of natural products. The following examples highlight the possibilities provided by these reactions for solving some synthetic problems in this field.

The key step in the synthesis of nordehydrobufotenine (Scheme 140) was the VNS cyanomethylation of 5-bromo-2-nitroanisole. The formed arylacetonitrile was then alkylated with ethyl bromoacetate, and the product was subjected to reduction leading to 1,2,3,4-tetrahydro-4-cyano-2-quinolinone, which was subsequently nitrated. The obtained nitro derivative was transformed into the target compound via standard operations.[343]

The reaction of tricyclic sulfonamide, produced via nucleophilic substitution of hydrogen (Scheme 131), with cyanide anion leads to pyrrolo[4,3,2-*de*]quinolin-2(1*H*)-one, which then subjected to two consecutive reductions with $NaBH_4-NiCl_2$ and DIBAL-H is converted into 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline, an important fragment of marine alkaloids (Scheme 141).[324]

The VNS cyanomethylation of allyl 2-bromo-4-nitrophenyl ether was employed as the crucial step in the synthesis of benz[*cd*]indole derivative (Scheme 142).[295]

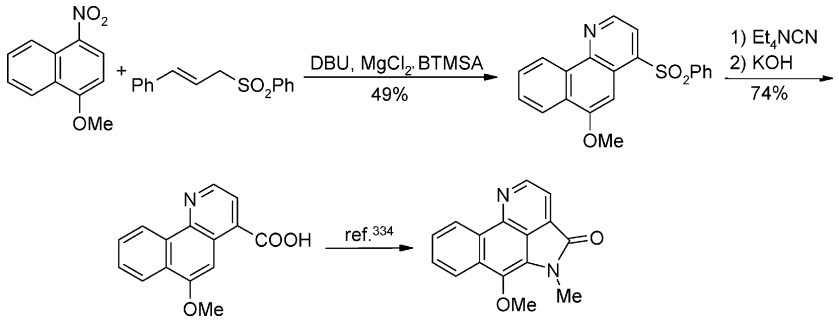
Another example of the application of VNS in synthesis of natural products is the formal synthesis of eupolauramine, an azaphenanthrene alkaloid isolated from the bark of African plant *Eupomatia laurina*. In our approach[344] the ester, obtained via VNS in 1-methoxy-4-nitronaphthalene with *tert*-butyl chloroacetate, was used as a starting material (Scheme 143). In a few steps this ester was transformed into azaphenanthrene; from that the eupolauramine can be obtained following the known procedure.[345]

Recently a much simpler approach to eupolauramine was developed.[58] Reaction of 1-methoxy-4-nitronaphthalene with cinnamyl phenyl sulfone in the presence of DBU, magnesium chloride, and bis(trimethylsilyl)acetamide (BTMSA) leads to 6-methoxy-4-(phenylsulfonyl)benzo[*h*]quinoline, which was transformed into benzoquinolinecarboxylic acid by substitution of the phenylsulfonyl with cyano group[324] followed by hydrolysis (Scheme 144). Further nitration and cyclization of oxindole ring according to the known procedure[345] led to eupolauramine.

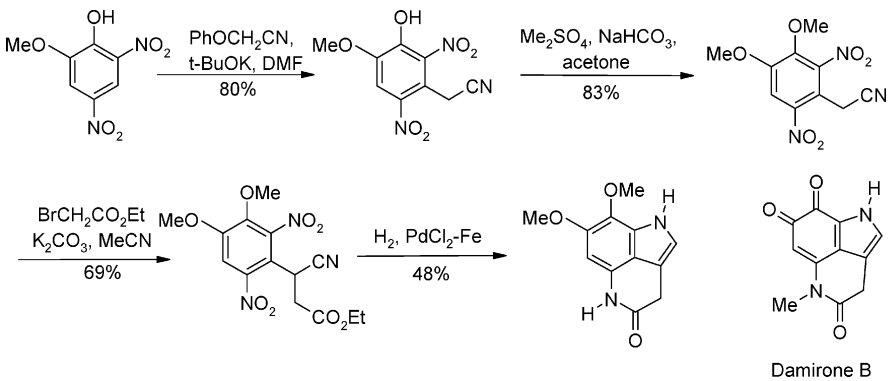
In the key step of the synthesis of damirone B precursor, specific orientation of VNS in 2,4-dinitrophenol was used.[73] Namely, 4,6-dinitroguaiacol was cyanomethylated with phenoxyacetonitrile selectively in the 5 position. Subsequent standard transformations gave the desired compound (Scheme 145).[346]

ONSH was employed as the key step in the synthesis of makaluvamine C, a neoplastic agent isolated from marine sponges.[347,348] The synthesis started

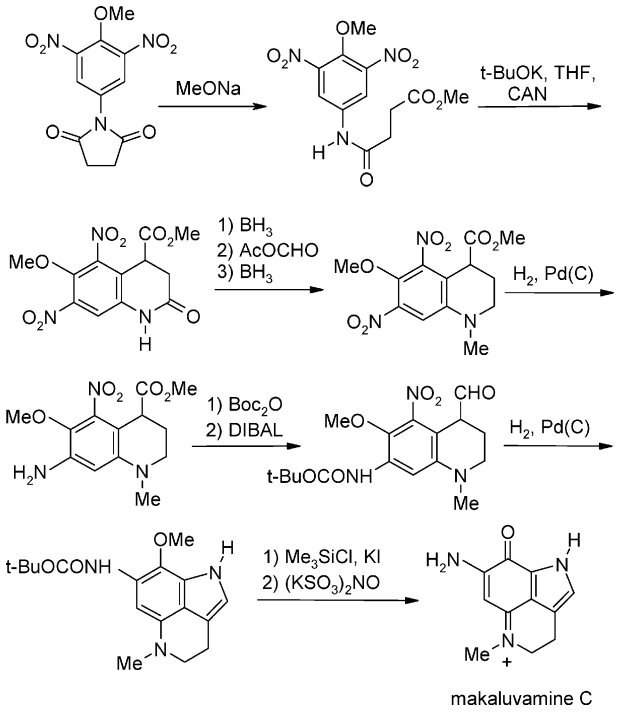
Scheme 144



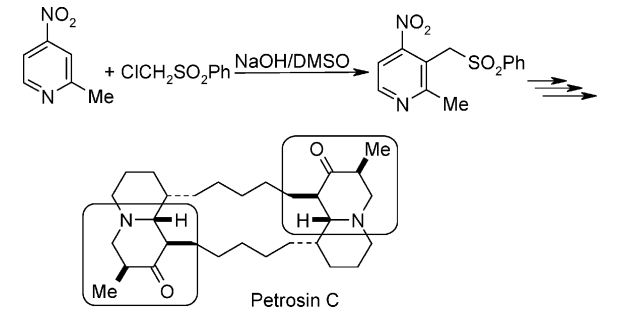
Scheme 145



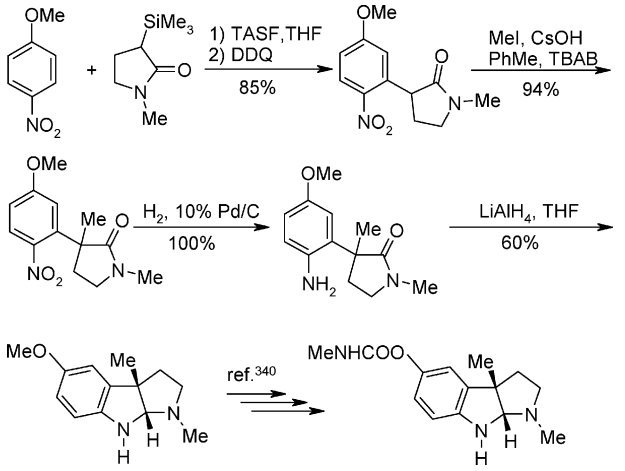
Scheme 146



Scheme 147



Scheme 148



from easily available *N*-(3,5-dinitro-4-methoxyphenyl)succinimide, which opens with sodium methoxide to an amido ester. This compound undergoes intramolecular oxidative nucleophilic substitution of hydrogen in the presence of potassium *tert*-butoxide and cerium ammonium nitrate to give lactam. Further standard transformations lead to the makaluvamine C (Scheme 146).[347,348]

The product of the VNS in 2-methyl-4-nitropyridine with chloromethyl phenyl sulfone was used as a starting material for the synthesis of petrosins C and D (Scheme 147).[349]

In the formal total synthesis of D,L-physostigmine, the key intermediate was obtained in the reaction of 4-nitroanisole with 3-phenylpyrrolidin-2-one derivative following the fluoride-assisted ONSH protocol (Scheme 148).[350] Further steps included standard transformations to the tricyclic intermediate, from which the D,L-physostigmine was obtained following the known procedures.[351,352]

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