Topics in Heterocyclic Chemistry 37
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Valery Charushin
Oleg Chupakhin *Editors*

Metal Free C–H Functionalization of Aromatics

Nucleophilic Displacement of Hydrogen

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37
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Valery Charushin • Oleg Chupakhin
Editors

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Nucleophilic Displacement of Hydrogen

With contributions by
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Preface

One of the current trends in development of both academic and industrial organic synthesis is orientation of chemists on using "chlorine-free" ecologically benign processes, based on direct methods of C–H functionalization of aromatic compounds, avoiding halogenated starting materials or intermediates.

The synthesis and structural modifications of aromatic systems have always been a subject of considerable interest to many chemists. Electrophilic aromatic substitution of hydrogen S_EAr and nucleophilic aromatic substitution of halogen and other good leaving anionic groups S_NAr^{ipso}, became the main synthetic methodologies and basic industrial processes of the last century. For many decades they have been exploited by chemists to obtain enormous number of derivatives of this important class of organic compounds.

A great variety of effective metal-catalyzed cross-coupling reactions (Heck, Stille, Suzuki-Mijaura, Sonogashira, Kumada, Negishi, Buchwald-Hartwig, Hijama, and others) have been advanced during the last three decades, however most of these catalytic methods are also based on using aryl halogenides, as starting materials. The situation is far from ideal from an atom economy point of view (for instance, bromination of aromatics – debromination), to say nothing of its poor correspondence to other principles of the green chemistry. Besides that, metal-catalyzed cross-coupling reactions often require the presence of palladium-containing catalysts and phosphorus-containing ligands, traces of which could not be admitted in pharmaceutical products. This is why the roundtable of leading global pharmaceutical companies, arranged by the American Chemical Society and Green Chemistry Institute, put the C–H activation of aromatics (including cross-coupling reactions, avoiding the preparation of haloaromatics) in the list of promising "aspirational" reactions (for detail see: [1]).

We believe that it is a high time to draw attention of both academic and industrial chemists to a relatively new synthetic methodology, which is based on the direct metal-free nucleophilic displacement of hydrogen in aromatic systems (S_N^H).

This volume of *Topics in Heterocyclic Chemistry* is composed of six chapters presented by an international set of authors, which responded to our proposal to

review the recently published data on the S_NH reactions, proceeding without organometallic intermediates.

The chapter "Metal-Free C–H Functionalization of Aromatic Compounds Through the Action of Nucleophilic Reagents" by Valery Charushin and Oleg Chupakhin (Postovsky Institute of Organic Synthesis; Ural Federal University, Ekaterinburg, Russia) presents a general concept of the S_NH reactions. It is supposed to demonstrate a common character of the S_NH reactions, as a fundamental property of aromatic and hetero-aromatic compounds, and to show the practical value of metal-free C–H functionalization of aromatics.

The chapter "Nucleophilic Substitution of Hydrogen in Arenes and Heteroarenes" by Mieczysław Mąkosza and Krzysztof Wojciechowski (Institute of Organic Chemistry, The Polish Academy of Sciences, Warsaw, Poland) provides us with the comprehensive review on both oxidative and eliminative versions of the S_NH reactions, including the so-called vicarious nucleophilic substitution, which appears to be a very essential part of the S_NH methodology. Indeed, the presence of a vicarious (auxiliary) group facilitates elimination of hydrogen with pair of electrons from the intermediate σ^H-adducts.

The chapter "Direct Functionalization of C–H Fragments in Nitroarenes as a Synthetic Pathway to Condensed N-Heterocycles", authored by Svyatoslav Shevelev and Alexey Starosotnikov (Zelinsky Institute of Organic Chemistry, Moscow, Russia), deals with the direct functionalization of C–H fragments in nitroarenes, followed by intramolecular cyclizations, as an effective synthetic pathway to condensed nitrogen heterocycles.

The chapter "C–H Functionalizations of Heteroaromatic N-Oxides", prepared by Yoshinori Kondo (Tohoku University, Sendai, Japan), gives an excellent account of the recent advances in the field of nucleophilic C–H functionalization of heteroaromatic N-oxides, by using metal-free S_NH processes, as attractive environmentally benign methods of organic synthesis.

The chapter "The S_NH-Amination of Aromatic Compounds", authored by Anna Gulevskaya and Alexander Pozharsky (Rostov-on-Don University, Russia), presents a comprehensive review on the direct S_NH amination of electron-deficient heteroaromatic compounds. Recent advances in this area and many new aspects of the S_NH amination are discussed, including new types of reagents, metal-free catalysts, solvents and the hydride ion acceptors. The review shows that the S_NH amination is rather promising synthetic alternative to both classic and transition metal-catalyzed amino-dehalogenation reactions.

Finally, the chapter "Electrochemical C–H Functionalization of Arenes " by Iluminada Gallardo and Gonzalo Guirado (University of Barcelona, Spain) provide us with an excellent review showing a practical importance of electrochemical methods for the direct C–H functionalization of aromatic and heteroaromatic compounds – a very promising area that has been advanced significantly by these authors.

It is worth noting that three chapters of this volume have been written by the Russian chemists, and it seems to be a good opportunity to discuss the results

obtained by these research groups and to reflect properly a considerable body of the data on the $S_N{}^H$ reactions published in the Russian chemical journals.

We believe that numerous examples and methods for the direct metal-free C–H functionalization of arenes and heteroarenes, presented by an international team of chemists in six chapters of this volume, are not only complementary to each other, but also create the whole picture of the $S_N{}^H$ reactions, enabling one to estimate their current scope, synthetic potential and value as "chlorine-free" ecologically benign processes.

In conclusion, we would like to express our sincere gratitude to all authors for their valuable contributions. Also we are thankful to professor Bert Maes (University of Antwerp, Belgium), who encouraged us to prepare this volume, and Elizabeth Hawkins and Tanja Jaeger from Springer DE for their help and fruitful cooperation.

Finally, we are very much obliged to our families for their patience and understanding during preparation of the manuscript.

Ekaterinburg, Russia
9 December 2013

Valery Charushin and Oleg Chupakhin

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Metal-Free C–H Functionalization of Aromatic Compounds Through the Action of Nucleophilic Reagents

Valery N. Charushin and Oleg N. Chupakhin

Abstract During the past two decades the classical concept of nucleophilic aromatic substitution ($S_N^{ipso}Ar$) has been complemented with a new synthetic methodology (S_N^HAr or briefly S_N^H), enabling one to perform direct functionalization of aromatic C–H bonds and to build new carbon–carbon C(sp^2)–C(sp^3), C(sp^2)–C(sp^2), and C(sp^2)–C(sp) or carbon–heteroatom C(sp^2)–X bonds (X is O–, N–, P–, S–, Si–, halogen) through nucleophilic displacement of hydrogen in aromatic and heteroaromatic compounds.

Keywords Nucleophilic functionalization of aromatic C–H bonds · Nucleophilic addition · Nucleophilic displacement of hydrogen · Arenes · Arene–metal complexes · Azines · Azoles · σ^H-Adducts · Oxidative and eliminative versions of the S_N^H reactions · Mechanisms of the S_N^H reactions

Contents

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Abbreviations

Ar	Aryl
Bu	Butyl
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EEP	Electron–electron–proton sequence
EPE	Electron–proton–electron sequence
Et	Ethyl
i-Pr	*Iso*-propyl
Me	Methyl
NMR	Nuclear magnetic resonance
Nu	Nucleophile
PEE	Proton–electron–electron sequence
Ph	Phenyl
SET	Single electron transfer
S_N^H	Nucleophilic aromatic substitution of hydrogen
S_N^H(AE)	Addition–elimination protocol for the S_N^H reactions
S_N^H(AO)	Addition–oxidation protocol for the S_N^H reactions
S_N^X	Nucleophilic aromatic substitution of halogen X or other good leaving groups
t-Bu	*Tert*-butyl
THF	Tetrahydrofuran

1 Introduction

Aromatic and heteroaromatic compounds belong to one of the most important classes of organic compounds. Regardless of natural or synthetic origin, numerous derivatives of arenes and heteroarenes proved to be extremely important for industry, medicine, and agriculture. This is why a great deal of methods to incorporate various substituents into aromatic and heteroaromatic rings are now available in the literature, including excellent textbooks and monographs [1–11]. Nucleophilic aromatic substitution of hydrogen (S_N^H) is a relatively new synthetic methodology enabling one to functionalize directly C–H bond in π-deficient aromatic and heteroaromatic compounds through the action of a variety of carbon- or heteroatom-centered nucleophilic reagents (Scheme 1) [11–18].

Today it is clear that the S_N^H reactions undoubtedly belong to the key chemical processes, and the classical concept of nucleophilic aromatic substitution ($S_N^{ipso}Ar$) has to be complemented with a new synthetic methodology (S_N^H), which makes it possible to build a variety of new carbon–carbon C(sp^2)–C(sp^3), C(sp^2)–C(sp^2), and C(sp^2)–C(sp) or carbon–heteroatom C(sp^2)–X bonds (X is O–, N–P–, S–, halogen, etc.) through nucleophilic displacement of hydrogen in aromatic and heteroaromatic compounds. A great deal of the data on nucleophilic C–H functionalizations of arenes and hetarenes have been accumulated in the literature during the last two to three decades, including books [5, 11] and rather impressive list of review articles [11–49], demonstrating a common character of the S_N^H reactions, as a fundamental property of aromatic and heteroaromatic compounds.

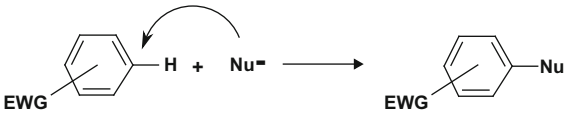
It is well known that aromatic compounds have a profound tendency to undergo a variety of substitution reactions, initiated by either electrophilic or nucleophilic attack on the C(sp^2) carbons of an aromatic ring.

Electrophilic aromatic substitution of hydrogen (for which the symbol S_EAr is usually used, while H is omitted) is a well-developed synthetic procedure which is widely used for structural modification of aromatic compounds [1].

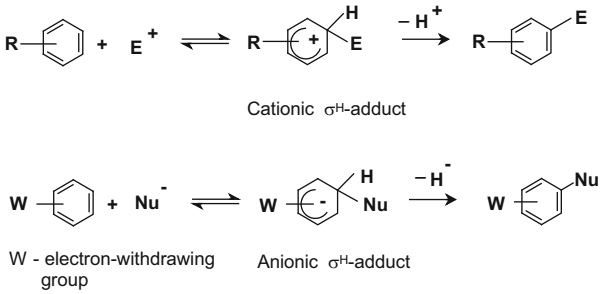
In the S_EAr reactions, the cationic character of intermediate σ^H-adducts facilitates elimination of a proton, and cleavage of the C(sp^3)–H bond takes place easily, enabling the system to restore the lost aromaticity (Scheme 2) [1].

This is not the case with the anionic σ^H-adducts which are derived from a nucleophilic attack at the unsubstituted carbon of an aromatic ring. Due to difficulties associated with the elimination of hydrogen with pair of electrons from anionic σ^H-adducts (in summary, the hydride ion), development of the S_N^HAr methodology has been lagged behind the S_EAr, $S_E^{ipso}Ar$, and $S_N^{ipso}Ar$ (S_N^XAr or S_N^X) reactions (where X is a group having a good leaving ability in an anionic form) for a long time [1]. A remarkable progress in studying of both oxidative and eliminative versions of the S_N^H reactions has been achieved only during the last two to three decades [11–49].

Although a great deal of methods to modify the structure of aromatic compounds through interaction with nucleophilic agents are now available in the literature, a large part of synthetic procedures exploited by chemists are based on use of



Scheme 1 Nucleophilic aromatic substitution of hydrogen

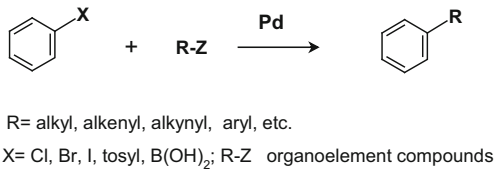


Scheme 2 Electrophilic and nucleophilic substitutions of hydrogen

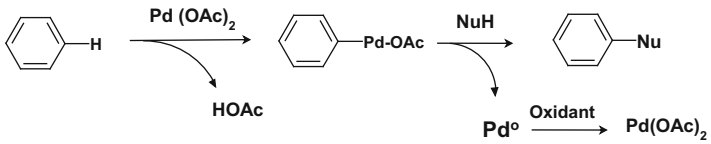
halogenated starting materials or intermediates [1–3, 5]. Indeed, in order to modify their structure the industrial organic synthesis often exploits pre-functionalization procedure, which is based on electrophilic chlorination, followed by a nucleophilic displacement reaction $S_N^{ipso}Ar$, accompanied by the loss of the chloride anion. The situation is far from ideal from a chemical point of view (chlorination–dechlorination), to say nothing of its poor correspondence to the green chemistry principles [7]. Nevertheless, it should be admitted that nucleophilic displacement of good leaving anionic groups $S_N^{ipso}Ar$ is one of the classical methods for incorporating substituents into an electron-deficient aromatic ring. This is the case where the nature of nucleophile and electronic character of the leaving group correspond to each other.

Another powerful synthetic tool of the advanced chemistry of aromatic compounds is a set of the metal-catalyzed cross-coupling reactions enabling one to build a variety of C(sp^2)–C or C(sp^2)–X (X is a heteroatom) bonds [8, 9, 50]. These methods are known as the Heck, Stille, Suzuki–Miyaura, Sonogashira, Kumada, Negishi, Buchwald–Hartwig, Hijama, and other name reactions [51]. Most of them are also based on use of aryl halogenides and palladium-containing catalysts and phosphorus-containing ligands (Scheme 3) [8].

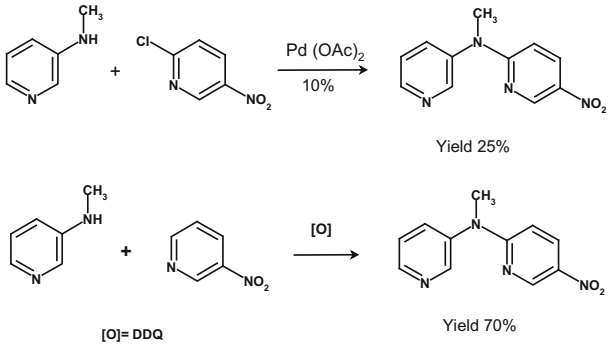
As far as activation of the C–H bond in aromatic compounds with palladium(II) is concerned, the features of these catalytic reactions are the following: (1) hydrogen atom is departed at the first step as a proton; (2) electrons of the activated C–H bond are involved in the formation of organopalladium intermediate; (3) palladium(II) is reduced into palladium (O), which then undergoes oxidation with an external oxidant into palladium(II) acetate, thus providing a cyclic catalytic process (Scheme 4).



Scheme 3 Palladium-catalyzed cross-coupling reactions of aromatics



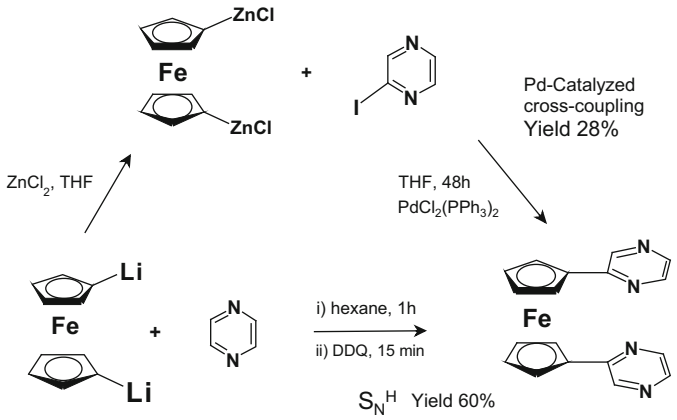
Scheme 4 The features of palladium-catalyzed cross-coupling reactions



Scheme 5 Palladium-catalyzed and metal-free amination of 3-nitropyridine

The metal-catalyzed cross-coupling reactions of aromatic compounds (especially, aryl halogenides) seem to be unprecedentedly popular among organic chemists, and many researchers prefer to use this methodology even in those cases, where application of this methodology is associated with some difficulties to incorporate halogen atoms into an aromatic ring. Indeed, when comparing reaction conditions and yields of 2-(*N*-methyl-*N*-pyridyl-3′)amino-5-nitropyridine, derived from palladium-catalyzed amino-dechlorination and metal-free amino-dehydrogenation of 3-nitropyridine (Scheme 5), one can see the advantage of nucleophilic aromatic substitution of hydrogen [52].

One of the key tasks of the advanced organic chemistry is to find direct routes for C–H functionalization of aromatic compounds, thus avoiding incorporation of halogen or other functionalities in order to correspond the principles of green chemistry. It is nicely illustrated by the example taken from ferrocene chemistry. Indeed, the lithium derivative of ferrocene proved to react smoothly with pyrazine



Scheme 6 Cross-coupling versus S_N^H in modification of pyrazines with ferrocene

in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidant to give the S_N^H product in a good yield (approx. 60%) under mild reaction conditions [53]. In order to modify ferrocene by means of palladium-catalyzed cross-coupling reactions, one has first to transform the lithium salt into the corresponding zinc compound and also to obtain iodopyrazine [54]. As a result, overall yield of this more complicated cross-coupling process proved to be much lower. Also, a number of steps in case of the direct S_N^H process is lower (Scheme 6) [53].

One of the advantages of the S_N^H methodology is that it provides new effective methods to build a variety of chemical bonds. Secondly, direct nucleophilic attack at C(sp^2)–H carbon enables one to avoid toxic chlorine-containing intermediates and to carry out chemical processes according to the principles of green chemistry, such as atom efficiency, preference for a shorter scheme of synthesis, waste prevention, use of less hazardous chemicals, and others [7, 43].

2 Historical Aspects of the S_N^H Reactions

Three to four decades ago a vast majority of textbooks on organic chemistry claimed that *hydrogen in an aromatic ring is not displaced with nucleophiles, because of a very strong basic character of the hydride ion* H^-. At that time nucleophilic aromatic substitutions were associated mainly with the *ipso*-attack at a ring carbon C(sp^2)–X bearing a halogen or other good leaving groups X ($S_N^{ipso}Ar$, $S_N^X Ar$, or briefly S_N^X). The first review on nucleophilic substitution of hydrogen was published in 1976 [12]. In this review it was suggested to use the symbols S_N^H in order to distinguish these reactions from the classical nucleophilic substitutions S_N^X [12]. Later a number of reviews have been published [13–49] and also the book *Nucleophilic Aromatic Substitution of Hydrogen* [11], which accumulated a

considerable body of data on conditions, kinetics, structure of intermediates, electrochemical and mathematic modeling, as well as plausible mechanisms and the general concept of the S_N^H reactions.

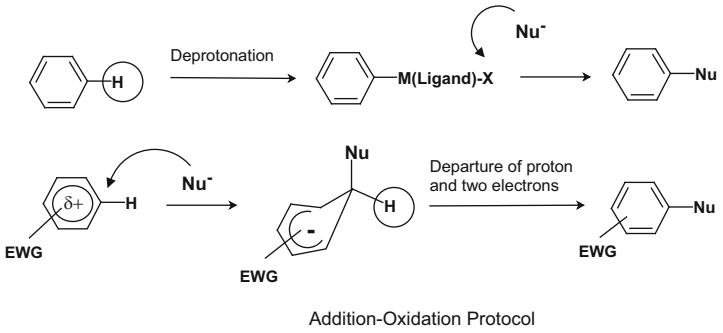
Many research groups contributed to the field of nucleophilic aromatic displacement of hydrogen. In particular, Prof. M. Makosza has developed the concept of the so-called vicarious nucleophilic substitution (VNS) [15–18, 27, 28, 36, 37, 41]. Indeed, the presence of vicarious (auxiliary) groups, facilitating elimination of hydrogen, is a very essential part of the S_N^H methodology [213]. Also we would like to mention the research groups of van der Plas [10, 19–21, 29, 35, 39, 40], Gulevskaya and Pozharsky [34, 45, 46, 48], which have modified the Chichibabin reaction and suggested to use very effective oxidative systems "liquid ammonia–potassium permanganate" and "alkylamine–silver permanganate–pyridine $AgPy_2MnO_4$" for amination of azaaromatics [216]. In the course of these studies, it has been shown that the S_N^H methodology is an efficient tool to build a variety of carbon–carbon and carbon–heteroatom chemical bonds between an aromatic ring and all kinds of N-, O-, S-, P-, Si-, and C-centered nucleophilic reagents [11–49]. This is why in the preface to his book on nucleophilic aromatic displacement reactions the distinguished chemist professor F. Terrier has named nucleophilic substitution of hydrogen in aromatic systems as ... *a fascinating subject of the last decade* [5].

Today we realize that a considerable body of data on the S_N^H reactions, which have been accumulated in the literature, cover a huge number of examples on direct functionalization of the C–H bond in aromatic and heteroaromatic compounds. In spite of the differences in the terminology and symbols used, nucleophilic aromatic substitution of hydrogen attracted attention of many chemists. Indeed, some authors refer to the S_N^H reactions as VNS of hydrogen [15–18, 27, 28, 36, 37, 41], while others use the terms S_NAr^H, S_N^H, oxidative nucleophilic substitution of hydrogen (ONSH) or nucleophilic aromatic substitution of hydrogen (NASH) [11–49]. We believe that the best description of these reactions is provided by the symbols S_N^HAr or more briefly S_N^H [11, 12], since they are in agreement with the systematization of reaction patterns accepted by chemical community [1, 10–21]. Also it is worth mentioning that Chap. 13 (Aromatic Substitution, Nucleophilic and Organometallic) of the latest edition of the March's textbook on advanced organic chemistry contains the section "Hydrogen as Leaving Group" [1].

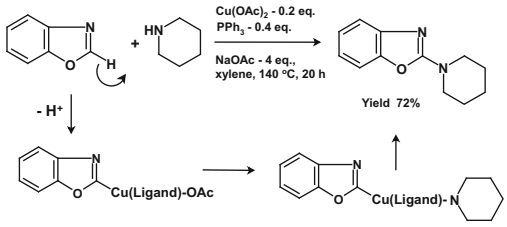
When analyzing the recently published data on aromatic substitution reactions, one has to admit that C–H functionalization of aromatic and heteroaromatic compounds becomes a highlight topic of many issues, and, indeed, it appears to be a very promising area of organic synthesis.

3 The Key Features and Scope of the S_N^H Reactions

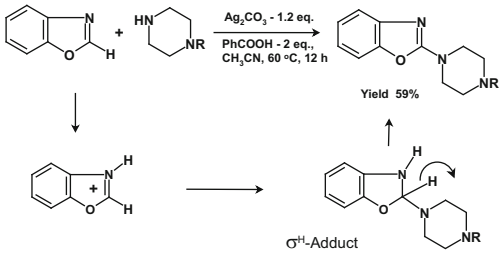
There are two principal approaches to incorporate nucleophilic fragments into an aromatic ring through the displacement of hydrogen. The first one is based on catalytic activation of the C–H bond, and it involves the step of deprotonation



Scheme 7 Functionalization of C–H bonds in aromatics



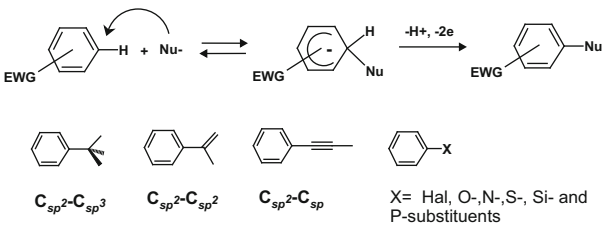
Scheme 8 Metal-catalyzed C–H functionalization of benzoxazoles



Scheme 9 Oxidative $S_N{}^H$ amination of benzoxazoles

followed by the formation of organometallic intermediates which then react with nucleophiles into the final products. The second approach ($S_N{}^H$) suggests a direct nucleophilic attack at unsubstituted carbon of an electron-deficient aromatic ring leading to σ^H-adducts followed by their oxidation and departure of a proton, the so-called addition–oxidation protocol $S_N{}^H$(AO) (Scheme 7).

Both schemes involve elimination of a proton, and the presence of an oxidant appears to be a necessary element of both reactions; however, the sequence and the activation ways are different, as illustrated by nucleophilic C–H functionalization of benzoxazoles (Schemes 8 and 9) [55].



Scheme 10 General scheme of the S_N^H reactions

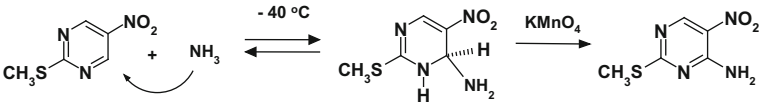
The first reaction is catalyzed by copper acetate, and it is supposed to involve two organocopper intermediates, while the C–H hydrogen atom is eliminated at the first step due to deprotonation (Scheme 8) [55].

Alternative procedure involves N-protonation, addition of the amino compound, and oxidation of the σ^H-adduct with silver carbonate. This scheme can be regarded as a typical example of oxidative nucleophilic aromatic substitution of hydrogen (S_N^H). It is worth to mention that hydrogen of the C–H bond is eliminated due to the oxidation procedure (Scheme 9) [55].

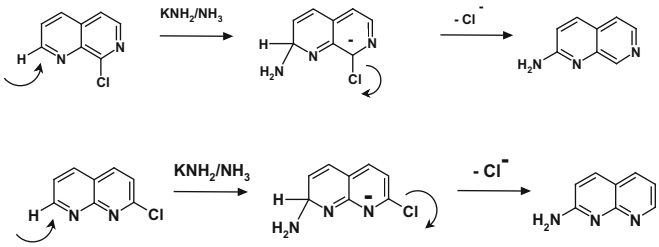
In the frames of this chapter we are going to focus on the features, scope, and limitations of the C–H functionalizations which are associated with activation of an aromatic ring for a direct nucleophilic attack and are free of any metal catalysis. This relatively new synthetic methodology is based on direct displacement of hydrogen (S_N^H) in π-deficient aromatic compounds by action of nucleophilic reagents. Cross-coupling C–H functionalizations of aromatic compounds dealing with metal-catalyzed activation of the C–H bond are well reflected in the literature [8, 9, 50, 51], and, therefore, they are beyond of consideration in this book.

The general scheme of the S_N^H reactions is somewhat similar to that of the $S_N^{ipso}Ar$, especially the first step of both types of S_NAr reactions which suggests interaction of π-deficient aromatic (heteroaromatic) compounds with nucleophiles. Electron-withdrawing groups, such as NO_2, N=O, C=O, cyano, and CF_3 are necessary to promote the ability of arenes for reacting with nucleophiles. A similar activation can be reached by incorporating of the aza group C=N–, other heteroatoms, and their cationic forms: $C{=}NR^+–$, $C{=}NH^+$, $=S^+–$, $=O^+–$, *N*-oxides $C{=}N^+–O^-$, etc. Indeed, all kinds of azinium, pyrilium, thiapyrilium, and tropylium cations as well as activated nitroannulenes, azaazulenes, arene–metal complexes and porphyrins, nitro- and aza-activated arenes, azoles and azines, and other π-deficient systems proved to be appropriate substrates for the S_N^H reactions (Scheme 10) [11–18].

π-Deficiency of aromatics is one of the requirements of the S_N^H reactions, limiting the scope of their application relative to that for metal-catalyzed cross-couplings. As for nucleophilic reagents for the S_N^H reactions are concerned, the later can be performed with a great deal of C-, O-, N-, P-, Si-, and S-centered nucleophiles, thus enabling one to carry out nucleophilic alkylation, alkenylation and alkynylation [1, 11, 24, 56, 57], amination, alkylamination and arylamination [1, 11, 19, 26, 29, 34, 39, 40, 45, 46, 58–74], hydroxylation and alkoxylation [75–77], cyanation [78–80], halogenations [81], as well as carboranylation



Scheme 11 Oxidative amination of 2-methylthio-5-nitropyrimidine



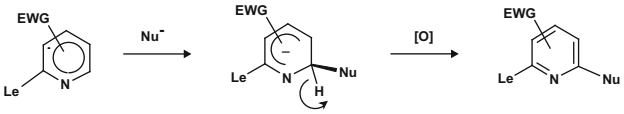
Scheme 12 Eliminative *tele*-S_N^H amination of 1,7- and 1,8-naphthyridines

[82, 83], ferrocenylation and cymantrenylation [53, 84–87], and other types of the S_N^H reactions.

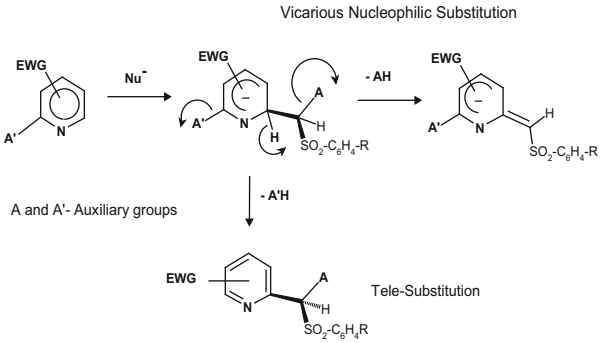
One of the key features of nucleophilic reactions in the series of aromatics is that C–H bonds are more vulnerable for nucleophilic attack than carbon atoms bearing heteroatom substituents X. This enables one to enhance functionality of organic compounds by direct displacement of C–H bonds in arenes and heteroarenes with retention of other functional groups in their molecules. For instance, 2-methylthio-5-nitropyrimidine undergoes oxidative amino-dehydrogenation reaction in liquid ammonia in the presence of potassium permanganate at position C-4, in spite of the presence of a good leaving group at the activated for a nucleophilic attack position C-2 (Scheme 11) [88].

Nucleophilic attack at unsubstituted carbon atom of an aromatic ring explains such phenomena as *cine*- and *tele*-substitution reactions. The S_N^H process in which a leaving group departs from a position vicinal to the addition site is named *cine*-substitution, while the S_N^H reactions in which a leaving group departs from a more remote position of the ring are classified as *tele*-substitution, as exemplified by nucleophilic displacement of chloro atom in 1,7- and 1,8-naphthyridines (Scheme 12). For many years these processes were regarded as abnormal *cine*- and *tele*-S_N^XAr transformations, to be in fact typical examples of the eliminative nucleophilic aromatic substitution of hydrogen, with a halogen atom playing the role of the vicarious (auxiliary) group [11–18].

A considerable body of the data on the S_N^H reactions accumulated in the literature [11–49] shows that these reactions are of fundamental value for the chemistry of electron-deficient arenes and heteroarenes. The S_N^H reactions can be realized through the following pathways: (1) the "addition–oxidation" protocol S_N^H(AO) which is based on using an outer oxidant (Scheme 13) [11–14] and (2) the "addition–elimination" scheme S_N^H(AE) which suggests the presence of



Scheme 13 Oxidative S_N^H(AO) reactions



Scheme 14 Eliminative S_N^H(AE) reactions

an auxiliary group either in a side chain of the intermediate σ^H-adducts (A) or in an aromatic ring (A′) (Scheme 14) [11, 15–18].

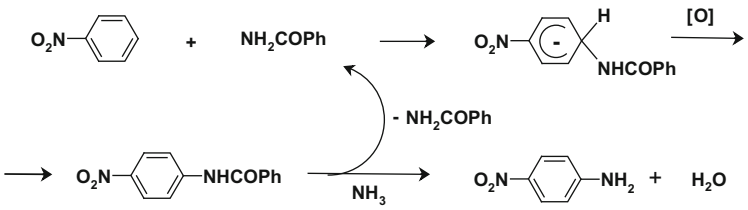
The S_N^H reactions of carbo- and heteroaromatic compounds with nucleophilic reagents, such as carbanions generated from arylsulfonyl derivatives R–C_6H_4–SO_2–CH_2–A, alkyl acetates ROOC–CH_2–A, and other C–H-active compounds bearing an auxiliary group A (A= Cl, OCH_3, SPh, etc.), are known as "vicarious" nucleophilic substitutions. This is due to the presence of a vicarious group A (A=Cl is generally the best), which is capable to depart in the anionic form, thus facilitating elimination of hydrogen as a proton (Scheme 14) [11, 15–18].

Many examples of VNS of hydrogen in nitro-substituted benzenes, pyridines, thiophenes, and other five- and six-membered heterocycles can be found in [213].

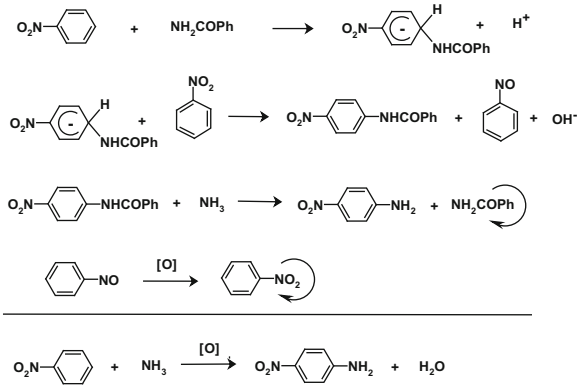
It is worth noting that both oxidative and eliminative schemes of the S_N^H reactions appear to be complementary to each other, since they have something in common: a proton and two electrons are departed from intermediate σ^H-adducts either by action of an oxidant (Scheme 13) or due to elimination of an auxiliary group (A or A′) (Scheme 14) [11–18].

3.1 Oxidative Version of the S_N^H Reactions

The key problem of all kinds of the S_N^H reactions is how to eliminate hydrogen with pair of electrons. External oxidant is usually needed to perform the S_N^H reactions; however, in some cases, highly electrophilic arenes can play the role of internal



Scheme 15 Amination of nitrobenzene with benzamide



Scheme 16 Chlorine-free synthesis of 4-nitroaniline

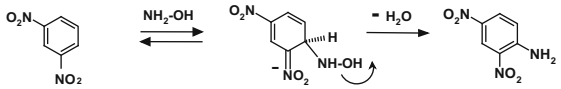
oxidant. A large-scale synthesis of *para*-nitroaniline from nitrobenzene and benzamide is a good illustration of industrial application of the S_N^H methodology and an excellent example of green chemistry (Scheme 15) [43, 89].

In this reaction the intermediate adduct is oxidized with nitrobenzene; the latter being transformed into nitroso compound and then is regenerated by air oxygen. Also benzamide is regenerated by ammonia. The total scheme for the amination process looks very simple and attractive (Scheme 16) [43, 89].

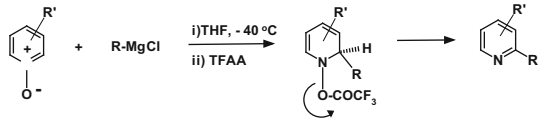
3.2 Eliminative Version of the S_N^H Reactions

Another principal mode of the S_N^H reactions is based on the eliminative way for transformation of σ^H-adducts, which is also known as *auto*-aromatization. In this case, two electrons are supposed to be taken from intermediate σ^H-adducts with the assistance of an auxiliary anionic group. Amination of dinitrobenzene with hydroxylamine is a typical example of the *auto*-aromatization reactions (Scheme 17) [11, 17, 18, 45].

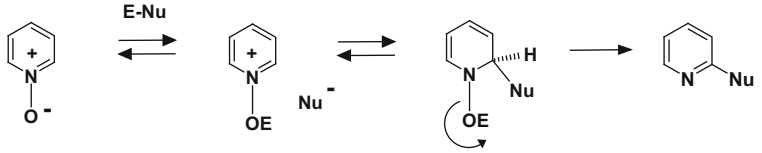
Eliminative S_N^H reactions are widespread in the chemistry of heteroaromatic compounds. It can be exemplified by transition-metal-free regioselective synthesis



Scheme 17 Eliminative S_N^H amination of 1,3-dinitrobenzene



Scheme 18 Regioselective synthesis of 2-substituted pyridines



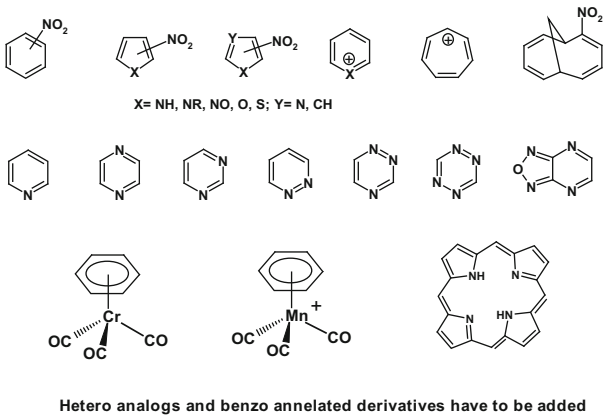
Scheme 19 Eliminative S_N^H reactions of azine *N*-oxides

of 2-substituted pyridines, achieved by reacting pyridine *N*-oxides with Grignard reagents at low temperatures (to avoid side reactions), followed by treatment with trifluoroacetic acid (TFAA) to cause elimination of hydrogen (Scheme 18) [90–93]. The formation of two pyridines from acylated pyridine *N*-oxides is a typical example of the *cine*-S_N^H substitution reactions [11, 45].

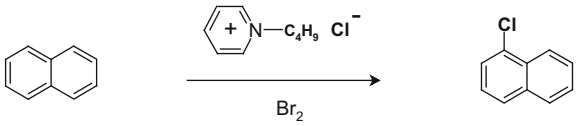
This feature of the S_N^H reactions of azine *N*-oxides is of a general character. Indeed, the so-called deoxygenative nucleophilic transformations of azine *N*-oxides and their cationic forms into S_N^H products have been established to involve the *auto*-aromatization step, in which the *N*-oxide, *N*-alkoxy, or *N*-acyloxy functions are auxiliary groups, facilitating elimination of hydrogen from the intermediate σ^H-adducts (Scheme 19) [11, 45, 90–93] (for more details [215]).

4 Aromatic and Heteroaromatic Substrates

The S_N^H reactions are of fundamental value for the chemistry of aromatic and heteroaromatic compounds. According to Prof. M. Makosza nucleophilic aromatic substitution of hydrogen is a general process of great practical value [17] and can be regarded as a new chapter of aromatic chemistry [18]. These reactions can be applied to a great number of nitroarenes and hetarenes, aza- and heteroaromatic compounds, including their benzo analogues, as well as metallabenzenes and arene–metal complexes, macrocyclic aromatics, and other types of electron-deficient substrates (Scheme 20).



Scheme 20 Structural patterns of compounds entering the S_N^H reactions



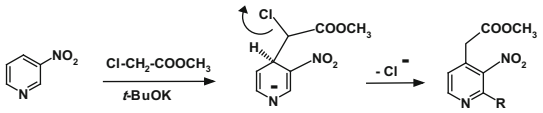
Scheme 21 Nucleophilic chlorination of naphthalene

4.1 Unactivated Arenes

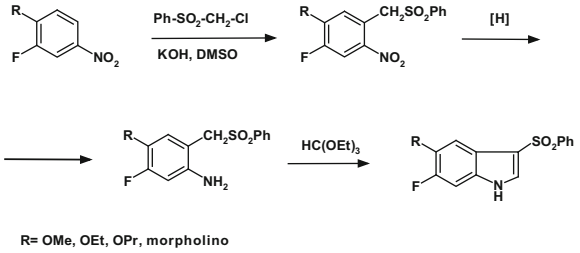
Being unactivated for a nucleophilic attack, benzene and naphthalene are very reluctant to undergo the S_N^H reactions. Indeed, nucleophilic substitution of hydrogen in the nonactivated benzene ring is a very rare phenomenon in organic chemistry, and these transformations usually require rather drastic reaction conditions [1, 11]. For instance, benzene undergoes nucleophilic alkylation on treatment with *t*-butyllithium in decalin at 165°C to give *t*-butylbenzene in a poor yield (15%) [11, 94]. Also naphthalene reacts with *t*-butyllithium under the same reaction conditions to give predominantly the monoalkylation product at the position 1 [11, 94]. However, it has recently been found that ionic liquids such as 1-*n*-butylpyridinium, 1-*n*-hexylpyridinium, or 1-*n*-decylpyridinium chlorides, containing bromine, are able to cause nucleophilic chloro-dehydrogenation of naphthalene at 100°C in the nitrogen atmosphere (Scheme 21) [81].

There are a few other examples of the S_N^H reactions in the series of unactivated arenes, such as nucleophilic methylation of anthracene and phenanthrene by action of dimethyl sulfoxide (DMSO) in the presence of a strong base (sodium hydride or potassium *t*-butoxide) [11, 95, 96]. However, it is clear that the addition of nucleophiles to such aromatic systems is a very unfavorable process, due to the

Scheme 22 Nucleophilic alkylation of 3-nitropyridine



Scheme 23 Synthesis of fluorine-containing indoles



loss of relatively high aromatic delocalization energies, whereas no electron-withdrawing substituents or heteroatoms stabilizing the formation of anionic σ^H-adducts are present in the ring.

4.2 *Arenes and Hetarenes Activated by the Nitro Group*

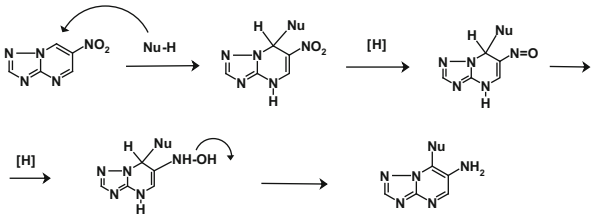
The nitro group in the *ortho*- or *para*-positions is one of the strongest electron-withdrawing substituent, activating an aromatic ring for a nucleophilic attack [5]. No wonder that a great deal of both oxidative and eliminative S_N^H reactions have been observed in the series of nitroaromatic compounds [11, 15–18, 25, 27, 28, 30–32, 36, 37, 97–100]. The VNS protocol has been particularly effective for the S_N^H reactions of a large number of nitro-substituted aromatic and heteroaromatic compounds [11–18, 25, 27, 28, 30–32, 36, 37, 45, 98–100], as illustrated by nucleophilic alkylation of 3-nitropyridine with vicarious methyl chloroacetate (Scheme 22) [100].

Another example for the application of the S_N^H methodology in the chemistry of nitroarenes is the synthesis of fluorine-containing indoles. It has been shown that substitution of hydrogen H-6 in 3-fluoro-4-*R*-substituted nitrobenzenes by the action of vicarious chloromethyl phenyl sulfone proceeds selectively in DMSO in the presence of KOH at room temperature to give 4-*R*-3-fluoro-6-(phenylsulfonyl-methyl)nitrobenzenes in 60–70% yields (Scheme 23) [101].

Cyclization of these compounds by action of diethyl maleinate results in the formation of diethyl 6-*R*-7-fluoroquinoline-2,3-dicarboxylates [102], while reduction of the nitro group followed by cyclization with triethyl orthoformate affords the corresponding fluorine-containing 3-phenylsulfonylindoles (Scheme 23) [101].

Aromatization of the σ^H-adducts is a crucial step in a vast majority of the S_N^H reactions, although sometimes it requires rather unusual conditions. It has been shown that aromatization of the σ^H-adducts derived from 6-nitro-1,2,4-triazolo

Scheme 24 Aromatization assisted by reduction of the nitro group



[1,5-*a*]pyrimidines can be assisted by the reduction of the nitro group in the dihydropyrimidine intermediate. In this particular case of the S_N^H reaction, a reductive agent is needed, instead of oxidant, to generate an auxiliary group. The most plausible mechanism of this *auto*-aromatization involves elimination of water from the intermediate σ^H-adduct, with the NH-hydroxy fragment acting as the auxiliary group. Finally, prototropic rearrangement of the heterocyclic imine affords the amino compound in good yield (Scheme 24) [103].

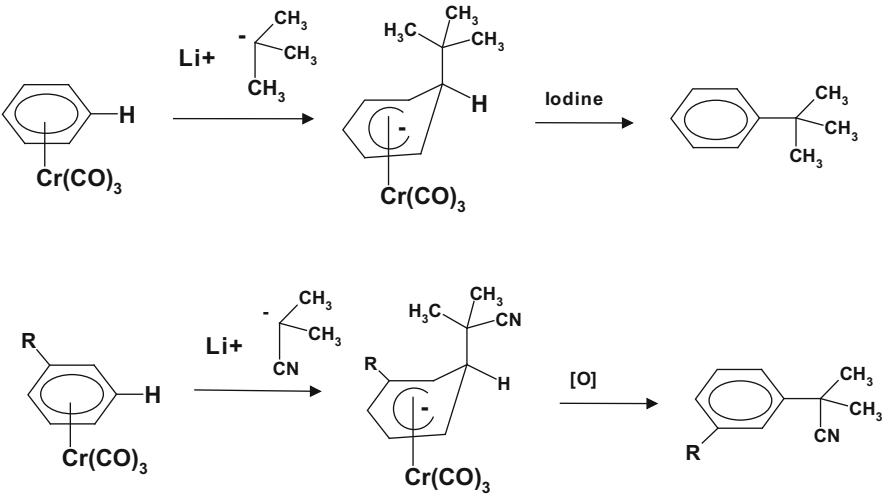
This method has been exploited for the synthesis of a variety of condensed heterocyclic systems through *auto*-aromatization of the intermediate σ^H-adducts derived from the reactions of nitro-substituted azoloazines with nucleophiles [104, 105].

4.3 Arene–Metal Complexes

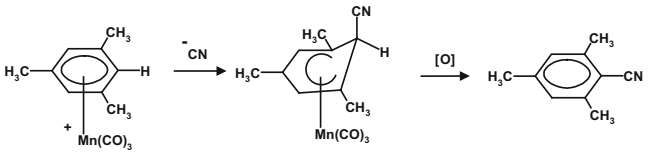
π-Coordination of aromatic compounds with transition metals enhances susceptibility of arene–metal complexes toward a nucleophilic attack. Indeed, arene–metal complexes are reactive with carbanions at low temperature (−78°C) to form rather stable adducts which can easily be oxidized into the corresponding S_N^H products [11, 106–112].

In particular, the chromium tricarbonyl unit proved to be a very suitable group for activation of arenes, since it can easily be attached to the benzene ring and later on be removed at the final step of the reaction [106–112]. It can be exemplified by the formation of *t*-butylbenzene in 68% yield on treatment of the benzenetricarbonylchromium complex with *t*-butyllithium in tetrahydrofuran (THF) at −78°C under argon atmosphere followed by oxidation of the intermediate σ^H-adduct with iodine at 0°C (Scheme 24) [108]. The tricarbonylchromium complexes of ethylbenzene and chlorobenzene proved to react with alkyllithium salts predominantly at the *meta*-position to give the corresponding *meta*-substituted alkylbenzenes, as might be expected for a nucleophilic reaction on the benzene ring bearing an electron-donating substituent (Scheme 25) [11, 106, 107, 112].

Also cationic complexes of arenes with iron, manganese, ruthenium, and osmium proved to be appropriate substrates for nucleophilic C–H functionalization according to the same addition–oxidation protocol S_N^H(AO), as illustrated by the reaction of cationic mesitylene-tricarbonylmanganese with the cyanide anion (Scheme 26) [11, 112].



Scheme 25 Nucleophilic alkylation of arenes through the formation of tricarbonylchromium complexes

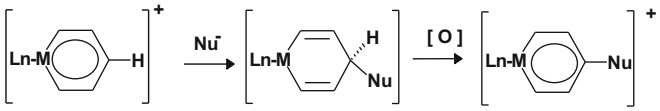


Scheme 26 Nucleophilic cyanation of mesitylene

4.4 Metallabenzenes

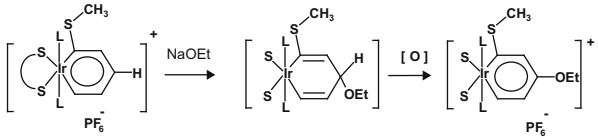
Functionalization of metallabenzenes through nucleophilic aromatic substitution of hydrogen is a new motif of the chemistry of aromatic compounds. Cationic osma- and iridabenzenes have recently been shown to undergo regioselective nucleophilic aromatic substitution of hydrogen at the position 4 relative to the metal in a two-step "addition–oxidation" process (Scheme 27) [113].

The first step in these transformations is the addition of nucleophiles, such as methyllithium and sodium ethoxide, resulting in the corresponding neutral osma- or iridacyclohexa-1,4-diene complexes. Oxidation of these σ^H-intermediates with oxidizing agents, such as oxygen, copper chloride, or DDQ, affords the final cationic $S_N{}^H$ products. This approach is demonstrated by the reaction of cationic iridabenzene with the ethoxide anion (Scheme 28) [113].



M - metal; Ln - ligand

Scheme 27 Nucleophilic substitution of hydrogen in metallabenzenes



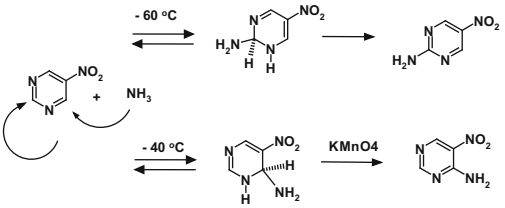
Scheme 28 Nucleophilic substitution of hydrogen in iridabenzene

4.5 Azines, Quaternary Azinium Salts, and Azine N-*Oxides*

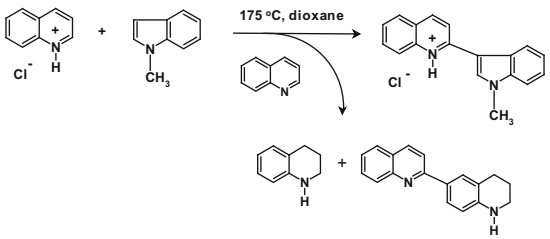
Six-membered azaaromatic compounds and especially their N-H, *N*-alkyl, and *N*-acyl azinium quaternary salts, as well as *N*-oxides and their *N*-*O*-alkyl and *N*-*O*-acyl cationic forms, are appropriate substrates for nucleophilic displacement of hydrogen [10–14, 19–24, 34, 35, 39, 40, 42, 43, 45, 114–117]. Indeed, due to electron-withdrawing effect of the aza moiety (the nitrogen atom of the pyridine type), being comparable with that of the nitro group, 2- and 4-positions relative to the ring nitrogen show an enhanced activity toward nucleophilic reagents [10–24, 34, 35, 39–42, 45, 114–117]. Indeed, 2- and 4-amino compounds are derived from the reaction of 5-nitropyrimidine with liquid ammonia in the presence of potassium permanganate, and it is worth noting that 2-amino-5-nitropyrimidine is formed under kinetically controlled reaction at −60°C, while the formation of thermodynamically more stable 4-amino-5-nitropyrimidine takes place at temperatures above −40°C (Scheme 29) [11, 21].

It has recently been discovered that 2-(1-methylindol-3-yl)quinoline is formed in a good yield on reacting quinoline with *N*-methylindole in the presence of hydrogen chloride in dioxane. Two equivalents of quinoline substrate (quinolinium hydrochloride + quinoline) are necessary for this reaction, since one equivalent of quinoline (or the NH-protonated quinolinium salt) acts as oxidant to abstract hydrogen atoms from the intermediate σ^H-adduct, thus giving the $S_N{}^H$ product and a mixture of 1,2,3,4-tetrahydroquinoline and 1′,2′,3′,4′-tetrahydro-2,6′-biquinoline (Scheme 30) [118].

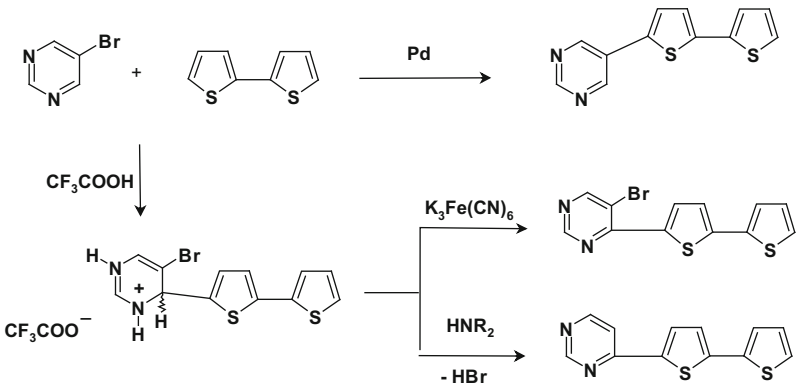
The chemistry of pyrimidines provides a number of examples showing that the $S_N{}^H$ reactions and Pd-catalyzed cross-couplings can be complementary to each other [119–122].



Scheme 29 S_N^H amination of 5-nitropyrimidine in liquid ammonia



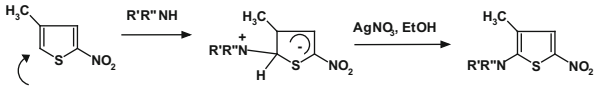
Scheme 30 Oxidative C–C coupling of quinoline with *N*-methylindole



Scheme 31 Incorporation of the dithiophenyl moiety in the pyrimidine ring

Indeed, a variety of heterocyclic compounds, such as thiophenes, dithiophenes, pyrroles, indoles, or carbazoles can be involved as carbon-centered nucleophiles in these reactions to modify the pyrimidine ring (Scheme 31) [120–122]. For instance, it has been shown that 5-bromopyrimidine reacts with dithiophene into the corresponding 5-substituted pyrimidine due to palladium-catalyzed aryl–aryl C–C cross-coupling reaction. On the other hand, 5-bromo-4-dithiophenyl-substituted pyrimidine was prepared from the same starting material through the S_H^N(addition–oxidation) reaction catalyzed by a Lewis acid in the presence of potassium

Scheme 32 Oxidative S_N^H(AO) amination of 5-nitrothiophenes



ferricyanide as oxidant. Also 4-dithiophenyl-substituted pyrimidine can be obtained from 5-bromopyrimidine due to the S_H^N(AE)*cine*-substitution reaction, proceeding according to the addition–elimination protocol. Thus, two positions of the pyrimidine ring, 4 and 5, can be modified through metal-catalyzed and metal-free S_N^H(AO) and S_N^H(AE) *cine*-substitution reactions of 5-bromopyrimidine with dithiophene (Scheme 31) [121].

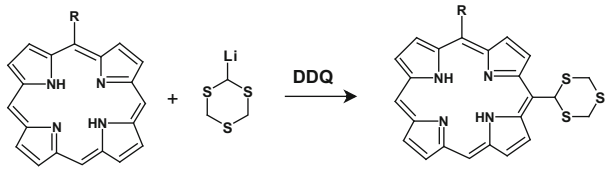
4.6 Azoles

Five-membered aromatic heterocycles, thiophenes, furans, pyrroles, and other π-excessive systems are reluctant, of course, to react with nucleophilic reagents. Contrary to that, nitro- or aza-activated derivatives of azoles undergo nucleophilic displacement of hydrogen rather smoothly. A great deal of both oxidative S_N^H(AO) and eliminative S_N^H(AE) reactions in the series of nitroazoles (nitropyrrole, nitrofuran, nitrothiophene) or aza-activated azoles (imidazoles, thiazoles, oxazoles), as well as their benzo analogues, have been documented in the literature [10–18, 45, 123–128].

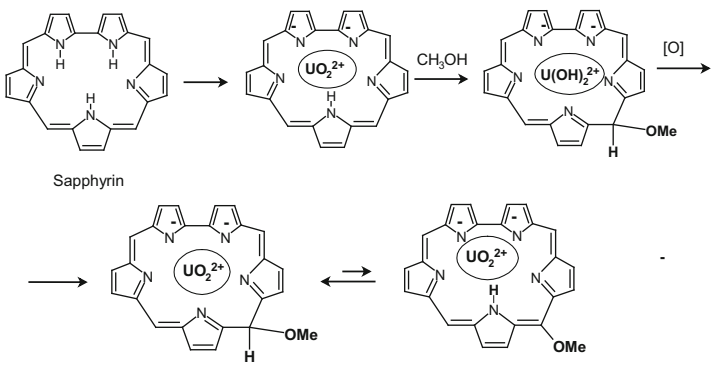
For example, the oxidative S_N^H(AO) reaction of 4-methyl-2-nitrothiophene with a variety of secondary amines (dimethyl- and diethylamines, *N*-benzylmethylamine, pyrrolidine, morpholine, and piperidine) proved to proceed smoothly on heating in ethanol (50°C) in the presence of silver nitrate to give amination products in moderate-to-good (30–75%) yields (Scheme 32) [128]. It has been established that the presence of 4-methyl (alkyl) group is very important for this S_N^H(AO) reaction to occur. Indeed, the 4-alkyl substituent appears to have a stabilizing effect on the intermediate σ^H-adduct, thus enhancing its lifetime, which is crucial for the oxidation step. This phenomenon is in striking contrast with the behavior of the parent 2-nitrothiophene which undergoes a ring-opening reaction under the same reaction conditions. Also it is noteworthy that the use of oxidants different from $AgNO_3$, such as cerium (IV) ammonium nitrate (CAN) or dichlorodicyano-1,4-benzoquinone (DDQ), afforded worse results (yields only 20–30%) [128].

4.7 Macroheterocycles

Substitution of hydrogen in porphyrins by action of carbanions (butyl or dithianyl lithium) in the presence of DDQ as oxidant is an interesting example of application of the S_N^H methodology in the chemistry of macrocycles, which seems to be rather



Scheme 33 Oxidative S_N^H(AO) alkylation of porphyrins



Scheme 34 Oxidative S_N^H(AO) methoxylation of sapphyrin

promising route to modify this important class of heterocyclic photosensitizers to obtain new derivatives for photodynamic therapy of cancer (Scheme 33) [129].

A rare and interesting example of ONSH with the methoxy group in the sapphyrin dioxouranium (VI) complex has been described (Scheme 34) [130, 131]. Sapphyrin (22-pentaphyrin[1,1,1,1,0]) has 22 electrons in the frames of its π-conjugated system, and it belongs to the expanded porphyrin family, thus allowing one to consider it as a macrocyclic aromatic compound.

Heating a mixture of free sapphyrin and methanol in pyridine/triethylamine solution for 72 h does not lead to substitution [130]. However, after the addition of the uranyl complex $(NMe_3)_2UO_2Cl_2$ in the presence of air oxygen, the reaction completes in 2 h to give a thermodynamically more stable tautomeric complex of uranyl and meso-methoxy substituted *iso*-sapphyrin. A plausible mechanism of this reaction is given below (Scheme 34) [131].

The introduction of the methoxy group to the sapphyrin ligand has been described as ONSH in the meso-bridge of the aromatic expanded porphyrin system with uranium (VI) as the oxidizing agent, although the role of uranium in this nucleophilic substitution is still under discussion [131]. It has been established that the uranyl dication within the ligand acts certainly as a strong electron-withdrawing group, thus activating the system for a nucleophilic attack. The addition of

methanol might be expected to change the oxidation state of the metal in the σ^H-adduct to uranium (IV). Also it is clear that uranium dication has a stabilizing effect on the formation of both σ^H-adduct and final S_N^H product (Scheme 34) [131].

5 Nucleophilic Reagents

Hundreds of carbon- and heteroatom-centered nucleophilic agents have been involved in S_N^H reactions, which proved to be both a convenient and powerful synthetic tool for application in heterocyclic and medicinal chemistry, polymer chemistry, and other branches of chemistry. It should be noted, however, that C-nucleophiles are still prevailing in the S_N^H reactions over heteroatom-centered ones because of the following reasons: (1) the C–C bond formation is one of the main of tasks of organic synthesis; (2) as a rule, the C-adducts are more stable in comparison with the σ^H-adducts derived from addition of heteroatom-centered nucleophiles to the same aromatic substrates.

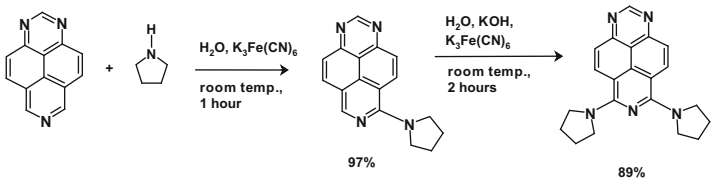
5.1 Nitrogen-Centered Nucleophiles

Nucleophilic amination of aromatic and heteroaromatic compounds appears to be one of the most important and well-studied S_N^H reactions [11–21, 26, 29, 34, 39, 40, 45, 46, 48, 58–74, 88]. This is why [216] prepared by professors A.V. Gulevskaya and A.F. Pozharskii (Rostov-on-Don University, Russia) is dedicated to amination of heteroaromatic compounds.

5.1.1 Ammonia, Primary, and Secondary Aliphatic Amines

Amination of pyridine on heating with sodium amide in refluxing xylene observed by Chichibabin and Zeide nearly 100 years ago [132] was probably the first successful example of amino-dehydrogenation in the series of π-deficient aromatic systems. However, rather drastic reaction conditions and a requirement for an appropriate oxidant for the classic Chichibabin amination did not stimulate chemists in earlier days to enter this field of S_N^H substitutions [23, 133, 134]. Later on, van der Plas with coworkers [11, 19–21, 29, 35, 39, 40, 88], Vorbruggen [26], Pozharskii, Gulevskaya, and Maes [34, 45, 46, 48, 67, 68, 71, 72], McGill and Rappa [23], Pagoria, Mitchell, and Shmidt [59, 61, 63], Lopyrev [65, 66], Katritzky [58], and many other researches [11, 21, 45, 55, 58–74] contributed to the field of S_N^H amination reactions.

New synthetic methodologies have been developed, making it possible to perform nucleophilic amination of aromatic and heteroaromatic compounds under mild conditions. In order to reach an effective amination of aromatic and



Scheme 35 Oxidative S_N^H amination of triazapyrene

heteroaromatic compounds, various oxidative aminative systems, such as "liquid ammonia–potassium permanganate" [11, 19–21, 29, 35, 39, 40, 88] and "alkylamine–*bis*(pyridine)silver(I)permanganate" [45, 46, 48, 67, 68, 71, 72] have been suggested. Also vicarious aminating agents, such as hydroxylamine [62], 4-amino-1,2,4-triazole (the vicarious leaving group is 1,2,4-triazole) [58, 62, 135], and 1,1,1-trimethyl hydrazinium iodide (the leaving group is trimethylamine) [62, 65, 66, 69, 70] have been used.

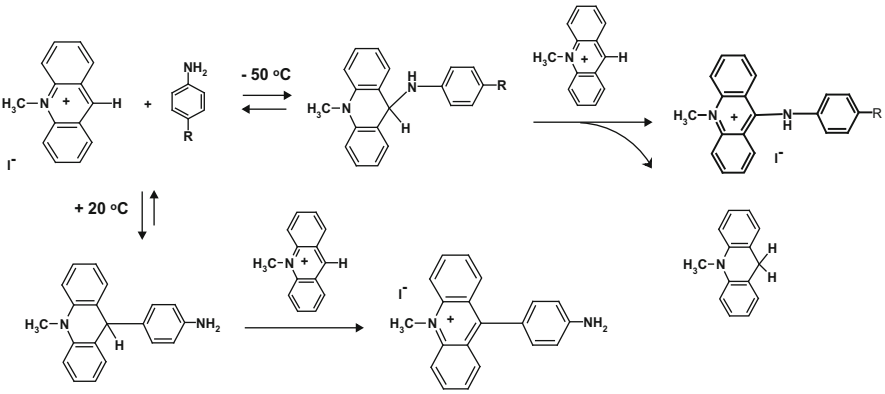
Incorporation of one or two fragments of pyrrolidine into triazapyrene in water in the presence of potassium ferricyanide demonstrates how effective is the application of the S_N^H methodology, which opens new opportunities in the field of amination of azaaromatic compounds (Scheme 35) [73].

5.1.2 Aromatic Amines as N-Nucleophiles

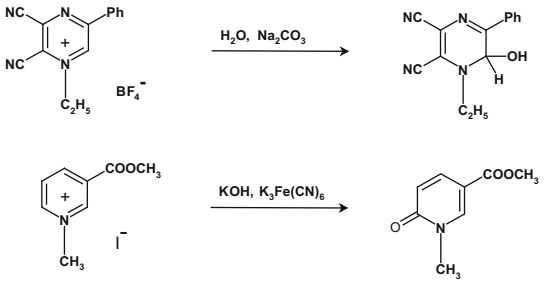
Due to their ambident nature, aromatic amines can exhibit properties of both C- or N-centered nucleophiles. It depends on a number of factors, such as electronic and sterical characteristics of arylamines, and also reaction conditions.

For instance, UV and nuclear magnetic resonance (NMR) studies of the reaction between *N*-methylacridinium ion and primary aromatic amines have revealed the formation of unstable N-adducts under kinetically controlled conditions (−50°C). Their formation is especially favored in case of anilines bearing in the *para*-position an electron-donating substituent R. At temperatures above 0°C, these N-adducts are gradually converted into thermodynamically more favored C-adducts. Also it has been shown that when no oxidant is added, the *N*-methylacridinium cation acts as oxidant of both N- and C-adducts, thus giving the corresponding S_N^H products and 10-methyl-9,10-dihydroacridine (Scheme 36) [11, 136].

It has to be mentioned that this scheme is in a full agreement with the data of kinetic and NMR studies [137].



Scheme 36 Arylamination versus aminoarylation of the acridinium ion



Scheme 37 Hydroxylation of *N*-alkylazinium ions

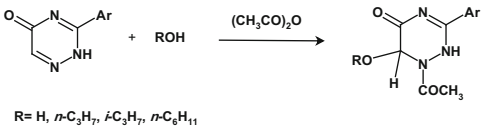
5.2 *Oxygen-Centered Nucleophiles*

Water is a week O-nucleophile; however, the hydroxide ion as well as alkoxides and phenolates are appropriate O-centered nucleophilic reagents for direct C–H functionalization of π-deficient arenes and hetarenes [1, 2, 10, 11].

5.2.1 Water

Many π-deficient azaaromatic compounds (pyridines, pyrimidines, pyrazines, triazines, pteridines, and so on) and especially their quaternary salts have a tendency to add water to give the corresponding σ^H-adducts [1, 2, 11, 114–117, 138]. A similar process of reversible pseudobase formation due to the addition of the hydroxide ion to *N*-alkylazinium [11], 1,4-diazinium [114, 138], and 1,2,4-triazinium [115–117] cations has been well documented in the literature. For instance, 3-phenyl-5,6-dicyano-1-ethylpyrazinium tetrafluoroborate easily adds water under basic conditions to give the corresponding 2-hydroxy adduct (Scheme 37) [138].

Scheme 38 Addition of alcohols to 3-aryl-1,2,4-triazin-5-ones



The hydroxy adducts can be oxidized into the S_N^H products. Indeed, the oxidative hydroxylation of *N*-alkylpyridinium salts into pyridones is a well-known S_N^H transformation, as illustrated by the reaction of 3-methoxycarbonyl-1-methylpyridinium iodide with the hydroxide ion in the presence of potassium ferricyanide, affording the corresponding 1-methyl-6-pyridone (Scheme 37) [2, 11, 139].

5.2.2 Alcohols

Stabilities of σ^H-adducts derived from nucleophilic addition of alcohols and alkoxide ions to azaaromatic compounds are varied to a great extent. A whole number of alkoxy adducts of 1,4-diazinium and 1,2,4-triazinium cations have been registered by NMR [114]; however, attempts to isolate them failed. Contrary to that, treatment of 3-aryl-1,2,4-triazin-5-ones with primary or secondary alcohols in the presence of acetic anhydride results in the formation of rather stable 6-alkoxy-1-acetyl-1,6-dihydro-1,2,4-triazin-5-ones (Scheme 38) [117, 140, 141].

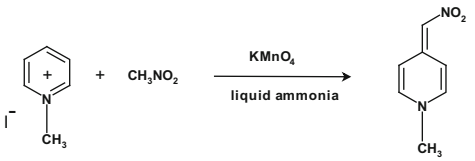
On the other hand, it has already been mentioned that under oxidative conditions alkoxide ions are able to cause C–H functionalization of aromatics, as exemplified by ethoxylation of iridabenzene (Scheme 28) [113] and methoxylation of macrocyclic sapphyrin (Scheme 34) [131].

5.3 Carbon-Centered Nucleophiles

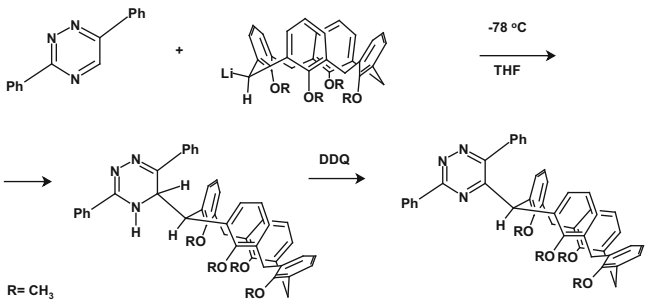
A great deal of carbanions, generated from C–H-active compounds, the Grignard reagents, the cyanide ion, all kinds of organometallic carbon–lithium derivatives, aromatic amines, phenols, pyrroles, indoles, thiophenes, furans, and other organic compounds with electron-rich carbon atoms have been involved in the S_N^H reactions as C-nucleophiles [1, 2, 10, 11, 114–117].

5.3.1 Carbanions Generated from C–H-Active Compounds

There are plenty of examples for the formation of σ^H-adducts derived from the nucleophilic attack by carbanions of C–H-active compounds at unsubstituted carbon atoms of nitroarenes, azines, azinium salts, and other types of aromatic and heteroaromatic compounds [1, 2, 10–18, 45, 114–117]. As a rule, the formed C-adducts can be identified spectroscopically, and in many cases, these



Scheme 39 Substitution of hydrogen in the *N*-methylpyridinium ion



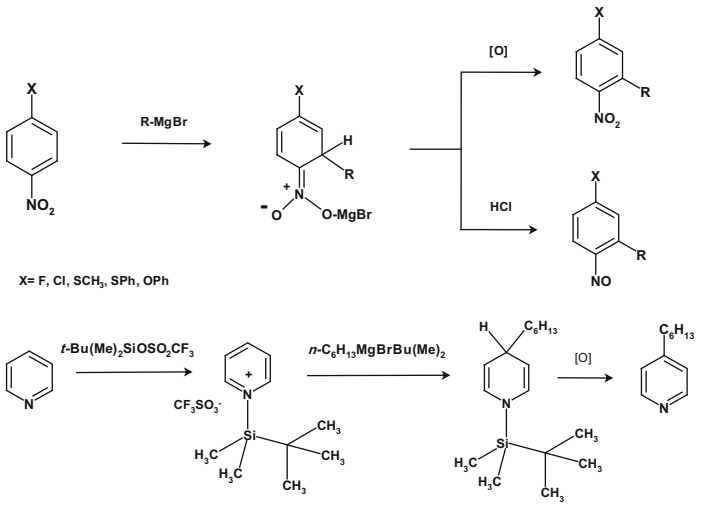
Scheme 40 S_N^H modification of the *meso*-position in calix[4]arenes

intermediate σ^H-adducts can be transformed into S_N^H products, provided an appropriate oxidant has been found. All kinds of carbanions, generated from nitroalkanes, alkyl ketones, alkyl cyanides, alkyl esters, dialkyl malonates, β-diketones, β-ketoesters, and other types of C–H-active compounds can be involved in these transformations. For instance, *N*-methylpyridinium iodide reacts with nitromethane in liquid ammonia in the presence of potassium permanganate to give the corresponding S_N^H product in 80% yield (Scheme 39) [142].

Also the lithium salts of macrocyclic compounds can be used as C-nucleophiles. Indeed, a new approach to modify the *meso*-position of tetramethoxy-substituted calix[4]arenes through the direct metal-free C–C cross-coupling of their lithium salts with 1,2,4-triazines has recently been suggested. It has been shown in our laboratory that the carbanions generated from tetraalkoxycalix[4]arenes are able to react easily with 3,6-diphenyl-1,2,4-triazine in THF at −78°C to give the σ^H-adduct at C-6 of the triazine ring. Oxidation of this C-adduct with DDQ at ambient temperature affords *meso*-substituted calixarene derivatives in good yields (Scheme 40).

5.3.2 Grignard Reagents

Grignard reagents are effective C-nucleophiles for incorporation of alkyl, aryl, and hetaryl substituents into aromatic and heteroaromatic rings. For instance, in the reaction of 4-substituted nitrobenzenes with the alkyl Grignard reagents, the



Scheme 41 S_N^H alkylation of nitroarenes and pyridine with Grignard reagents

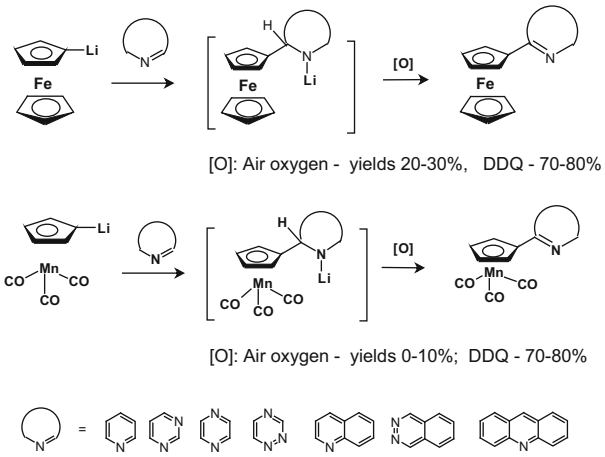
addition of RMgBr takes place exclusively at the *ortho*-position relative to the nitro group (Scheme 41). The nitronate σ^H-adducts of nitroarenes are relatively stable, particularly at lower temperatures; however, they are decomposed by the action of mineral acids into alkyl-substituted nitrosobenzenes due to *auto*-aromatization, or they can be oxidized with bromine, DDQ, or potassium permanganate into the corresponding nitrobenzenes (Scheme 40) [11–18, 143].

Other examples can be taken from the chemistry of 3- and 5-substituted 1,2,4-triazines, which easily add Grignard reagents exclusively at C-6 [11, 117, 144]. Also, activation of pyridine with *t*-butyldimethylsilyl triflate generates the corresponding pyridinium cation, which easily reacts with Grignard reagents exclusively at C-4 to give C-adducts, followed by their oxidation with air oxygen into 4-alkylpyridines (Scheme 41) [145].

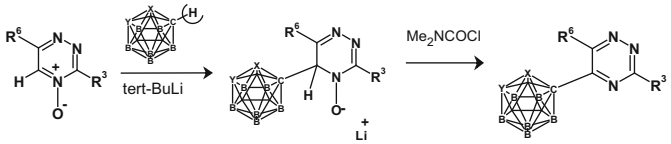
5.3.3 Carbanions Generated from Ferrocenes and Cymantrenes

The S_N^H methodology proved to be an effective synthetic tool to modify the structure ferrocenes and cymantrenes (Scheme 42) in order to obtain original ligands and organometallic complexes, including those possessing of planar chirality [53, 84–87, 146].

Also 6-ferrocenyl-substituted 2,2′-dipyridyl has been obtained by using the S_N^H methodology, and redox properties on new cobalt(II) and nickel(II) complexes of this ligand have been elucidated [147].



Scheme 42 S_N^H cross-coupling reactions of ferrocenes and cymantrenes



Scheme 43 Incorporation of carborane fragments into the triazine ring

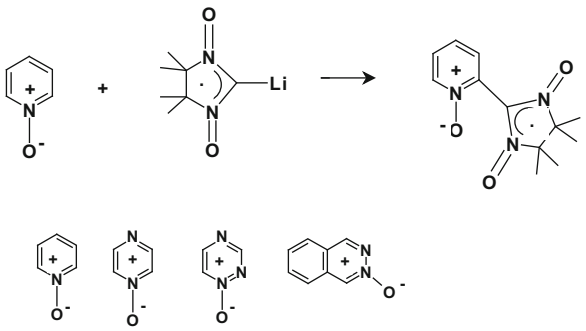
5.3.4 Carbanions Generated from Carboranes

It has recently been shown that carbanions generated from carboranes are able to substitute hydrogen in pyrazines, triazine-*N*-oxides, and other π-deficient systems. This original approach to incorporate boron-containing fragments into heterocyclic molecules proved to be rather effective for the synthesis of new ligands and also compounds which can be used for neutron-capture therapy of cancer (Scheme 43) [82, 83].

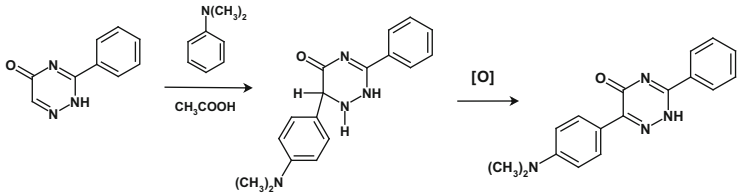
5.3.5 Carbanions Generated from Nitronyl Nitroxide Radicals

Free radical chemistry is another field of application of the S_N^H reactions. Lithium salts of nitronyl nitroxide radicals proved to be appropriate nucleophilic species to modify the structure of a number of azaaromatic compounds. This reaction provides an access to a new family of free radical compounds (Scheme 44) [148–150].

The reaction has been applied to a number of azaaromatic substrates, including pyrazine and quinoxaline mono- and di-*N*-oxides. The latter are able to undergo the double substitution of hydrogen, thus enabling one to incorporate two radical species into the S_N^H products [148–150].



Scheme 44 Incorporation of nitronyl nitroxides into the pyridine ring



Scheme 45 Aminoarylation of 1,2,4-triazin-5-one

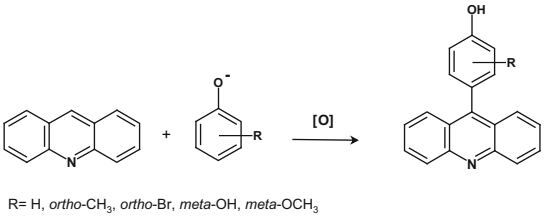
5.3.6 Aromatic Amines as C-Nucleophiles

A whole number of publications on the S_N^H reactions concern aminoarylation of highly π-deficient azaaromatic compounds, such as *N*-alkylacridinium salts [11, 136, 137], quinoxalin-2-ones, and quinazolin-2-ones [11, 12], as well as triazin-5-ones [117, 151]. For instance, 3-phenyl-1,2,4-triazin-5-one reacts with *N*,*N*-dimethylaniline on heating in acetic acid to give rather stable 3-phenyl-6-(4-*N*,*N*-dimethylaminophenyl)-1,6-dihydro-1,2,4-triazin-5-one, which can be oxidized by air oxygen, bubbling on reflux through the reaction solution in dimethylformamide (DMF), thus affording the corresponding S_N^H product in 52% yield (Scheme 45) [151].

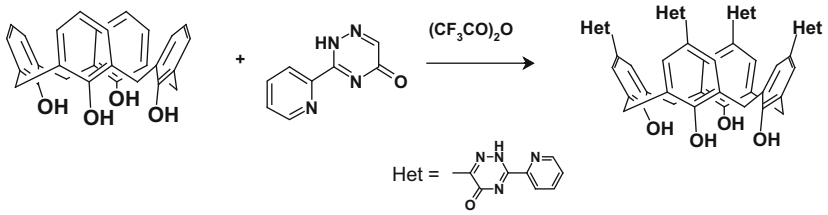
5.3.7 Phenols as C-Nucleophiles

When reacting with acridine in DMF at 130–140°C in the presence of air, bubbling through the reaction mixture, the ambident phenolate anions behave themselves as C-nucleophiles, thus giving the corresponding hydroxyarylation products (Scheme 46) [11, 12, 152].

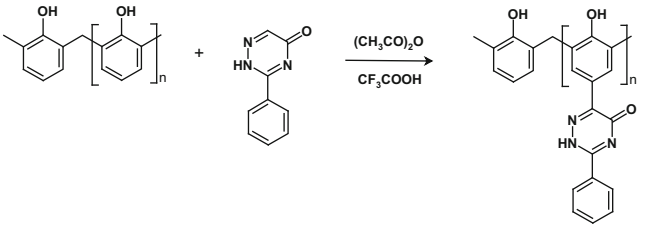
Since phenol fragments are present in many organic compounds of both natural and synthetic origin [1–4], the S_N^H methodology appears to be an appropriate tool



Scheme 46 Hydroxyarylation of acridine



Scheme 47 Modification of calyx[4]phenols by using the S_N^H methodology

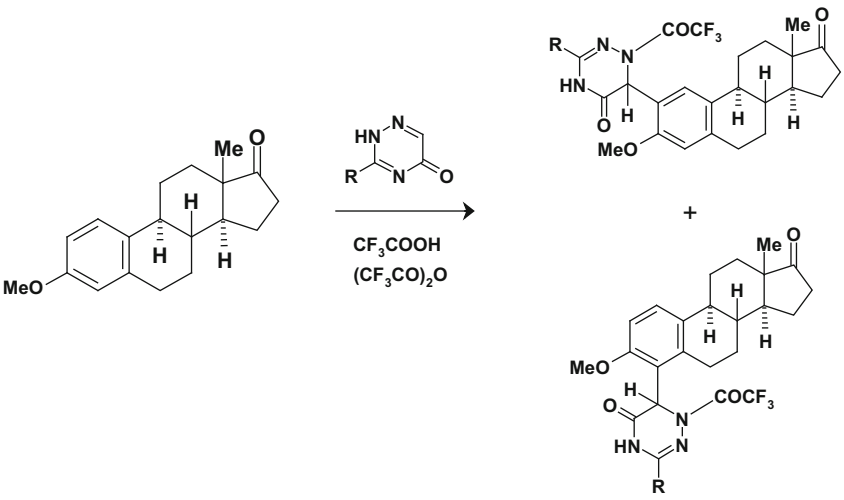


Scheme 48 Modification of phenolformaldehyde resins

for the formation of aryl–aryl C–C bond through direct cross-coupling reactions of phenols or phenolates with a variety of π-deficient aromatic and heteroaromatic compounds [11–14, 21].

Indeed, modification of the upper rim of calix[4]phenols through the S_N^H C–C coupling with electron-deficient triazinones is a new approach to change molecular cavities of these compounds, opening new possibilities for design of highly selective ligands (Scheme 47) [153]. The same approach has been applied to modify calixpyrroles and calixfurans [154–156].

Polymer chemistry is another field for application of the S_N^H methodology. It has recently been shown that phenolformaldehyde resins can be modified by reacting with 3-(pyridyl-2)-1,2,4-triazin-5-one. Incorporation of heterocyclic fragments in the structure of resins enabled to improve their selective sorption abilities toward Cu^{2+} and other ions of metals (Scheme 48) [157].



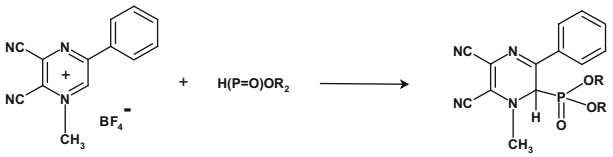
Scheme 49 Structural modification of steroids

Although the aryl–aryl C–C coupling of steroids, bearing the anisole fragment in their structure, with 1,2,4-triazinones results in the formation of two region-isomeric compounds, it demonstrates a successful application of the S_N^H methodology for C–H functionalization of this important class of bioregulators (Scheme 49) [158].

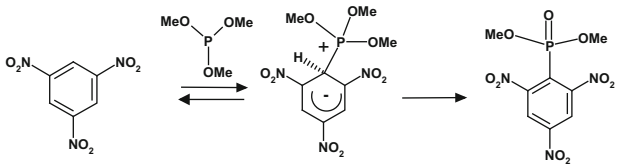
5.4 P-Nucleophiles

The data on the S_N^H reactions of phosphorus-centered nucleophiles with electrophilic nitroarenes and azines are scarcely available in the literature [11, 159] Although a number of σ^H-adducts derived from the addition of P-nucleophiles to isoquinoline [140], phthalazine [160], 4,7-phenanthroline [161, 162], *N*-alkylpyrazinium, and quinoxalinium salts [163] have been isolated and identified by NMR and X-ray crystallography, no attempts to convert these σ^H-adducts into the corresponding S_N^H products have been done. For instance, *N*-ethylpyrazinium tetrafluoroborate reacts with dialkyl and diaryl phosphonates under very mild conditions (room temperature, acetonitrile) to give stable dialkyl 3-phenyl-5,6-dicyano-1-ethyl-1,2-dihydropyrazin-2-yl phosphonates in good yields (Scheme 50) [163].

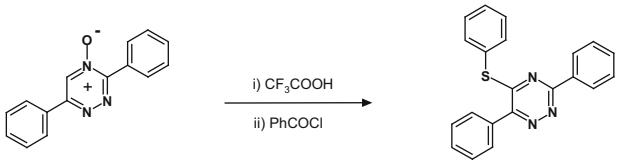
Substitution of hydrogen in 1,3,5-trinitrobenzene by action of trialkylphosphites, leading to picrylphosphonates, is a rare of the S_N^H reaction between nitroarenes and P-nucleophiles which can also be performed by using electrochemical oxidation (Scheme 51) [159, 164].



Scheme 50 Addition of dialkyl phosphonates 1-ethyl pyrazinium salts



Scheme 51 Synthesis of dimethyl picrylphosphonate



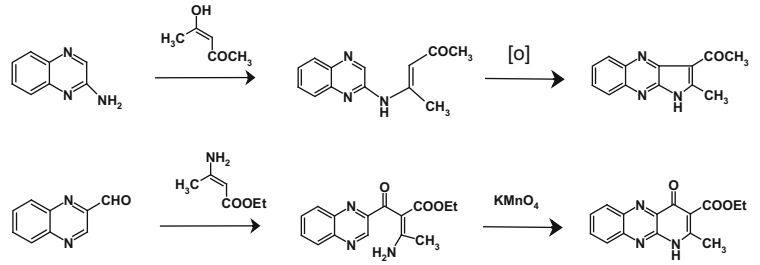
Scheme 52 C–H functionalization of 1,2,4-triazines with thiophenols

5.5 *S-Nucleophiles*

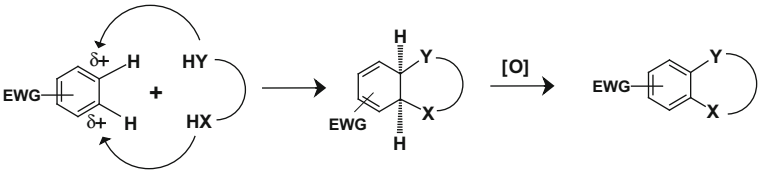
Treatment of 1,2,4-triazine 4-oxides with thiophenols in the presence of TFAA and benzoyl chloride affords 5-arylthio-1,2,4-triazines according to the S_N^H(AE) addition–elimination protocol (Scheme 52) [165].

6 Intramolecular S_N^H Reactions

An effective approach to condensed heterocyclic systems is the use of intramolecular nucleophilic substitution of hydrogen. The key role of the S_N^H step has been demonstrated by the synthesis of quinoxalines condensed with five- and six-membered heterocycles starting from 2-aminoquinoxaline [166] or quinoxaline-2-carbaldehyde [167, 168], correspondingly. Indeed, 2-aminoquinoxaline can be condensed with acetylacetone or other β-dicarbonyl compounds to give after oxidative intramolecular S_N^H reaction pyrrolo[2,3-*b*]quinoxalines in good yields (Scheme 52) [166]. Also condensation of quinoxaline aldehyde with ethyl



Scheme 53 Synthesis of condensed quinoxalines



Scheme 54 Use of tandem S_N^H–S_N^H reactions to obtain fused aromatic systems

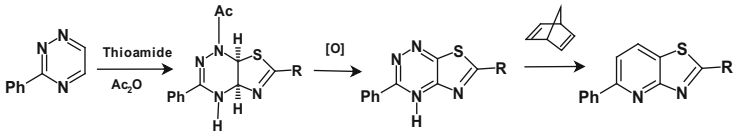
aminocrotonate affords the intermediate which is able to undergo the oxidative intramolecular S_N^H reaction, thus resulting in annelation of the pyridone fragment to quinoxaline skeleton (Scheme 53) [167, 168].

Also aromatic nitro compounds with the vacant *ortho*-position relative to the nitro group can be regarded as a good structural basis for the synthesis of condensed nitrogen heterocycles through cyclizations with this nitro group or by means of intramolecular displacement of the latter (for numerous examples of these transformations, [214], authored by professors Svyatoslav Shevelev and Alexey Starosotnikov).

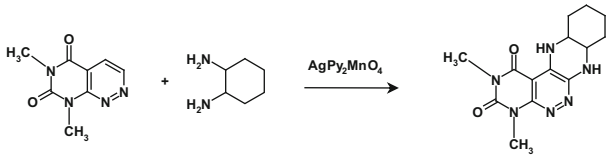
7 Tandem S_N^H–S_N^H, S_N^H–S_N^X, and S_N^H–Metal-Catalyzed Cross-Coupling Reactions

In addition to well-known routes to fused heterocyclic systems which are based on displacement of two leaving groups in an aromatic ring, it has been suggested to exploit tandem nucleophilic "addition–addition" (A_N–A_N), "addition–substitution of hydrogen" (A_N–S_N^H), and double substitution of hydrogen reactions (S_N^H–S_N^H) on two neighboring carbons (Scheme 54) [11, 114–116, 169–176].

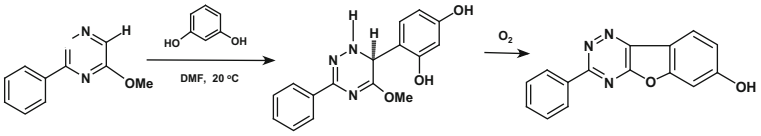
The synthesis of fused derivatives by using the tandem A_N–A_N, A_N–S_N^H and S_N^H–S_N^H reactions proved to be a very constructive approach [11, 114–116, 169–179]. A variety of 1,4-diazines condensed with five- and six-membered heterocycles have been obtained by reacting 1,4-diazinium (pyrazinium, quinoxalinium,



Scheme 55 Synthesis of thiazolo[4,5-*e*]1,2,4-triazines



Scheme 56 Tandem S_N^H–S_N^H cyclization of pyrimido[4,5-*c*]pyridazine

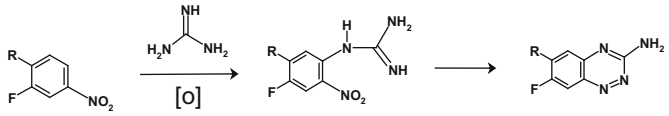


Scheme 57 The S_N^H–S_N^X synthesis of benzofuro[2,3-*e*]1,2,4-triazines

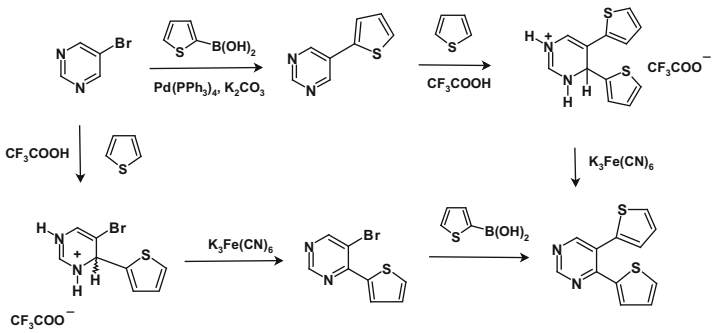
pyrido[2,3-*b*]pyrazinium, pteridinium, etc.) salts with enamines, diketones, ureas and thioureas, thiamides and thiohydrazides, dithiocarbamates, iminoesters, amidines, amidrazones, 1,2-diamines, amidoximes, and a lot of other 1,3- and 1,4-bifunc-tional nucleophiles [114–116, 169–181]. Also the tandem reactions of bifunctional nucleophiles at C-5 and C-6 of the 1,2,4-triazine ring proved to be an efficient route to condensed 1,2,4-triazines [115, 116, 174–178]. In particular, it has been found that the reaction of 3-phenyl-1,2,4-triazine, activated by acetic anhydride, with thioamides proceeds smoothly and regioselectively, leading to derivatives of ^{1}H-thiazolo[4,5-*e*]-1,2,4-triazines (Scheme 55) [179]. Also it has been shown that not only condensed 1,2,4-triazines but also fused pyridines can be obtained through the double addition of bifunctional nucleophiles to the triazine ring, followed by the double oxidation of C–H bonds and the ring transformation reaction (Scheme 55) [179].

A good example of the tandem oxidative S_N^H–S_N^H reactions is cyclization of 1,3-dimethylpyrimido[4,5-*c*]pyridazin-2,4-dione with 1,2-diaminocyclohexane, which takes place in the presence of the complex of silver permanganate with pyridine (Scheme 56) [180]. Other examples of the tandem S_N^H–S_N^H aminations of azaaromatic compounds are given in [216].

Nucleophilic substitution of hydrogen S_N^H can also be combined with the displacement of a good leaving group S_N^X, as illustrated by the reaction of 3-phenyl-5-methoxy-1,2,4-triazine with resorcinol, proceeding via the intermediate σ^H-adduct and affording benzofuro[2,3-*e*]-1,2,4-triazine according to the tandem S_N^H–S_N^X cyclization protocol (Scheme 57) [175].



Scheme 58 Synthesis of fluorinated benzotriazines

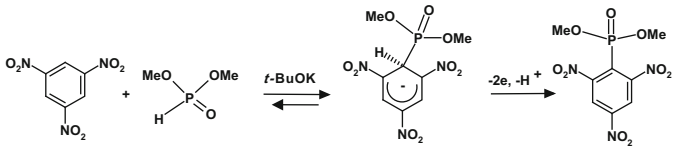


Scheme 59 Metal-catalyzed cross-coupling and metal-free S_N^H reactions

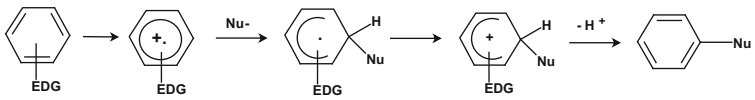
Also the synthesis of fluorinated 1,2,4-benzotriazines illustrates the advantage of the oxidative S_N^H reaction, as the key step in modification of fluorinated nitrobenzenes with guanidine followed by annelation of the 1,2,4-triazine ring (Scheme 58) [181].

The chemistry of azaaromatic compounds provides a number of interesting examples showing that the S_N^H reactions and Pd-catalyzed cross-couplings can be complementary to each other. For instance, combination of metal-catalyzed cross-coupling and metal-free nucleophilic aromatic substitution of hydrogen (S_N^H) reactions proved to be effective for the synthesis of 4- and/or 5-mono- or disubstituted pyrimidines [119–121]. Indeed, the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of 5-bromopyrimidine with 2-thienylboronic acid can be exploited to modify position 5 of the pyrimidine ring, while incorporation of the second thiophene moiety can be achieved through nucleophilic displacement of hydrogen at C-4, since this position of the pyrimidine ring is activated for a nucleophilic attack (Scheme 59) [119].

In summary, the examples given above show that metal-free S_N^H transformations are complementary to both classic S_N^X substitutions and metal-catalyzed cross-coupling reactions, and their combinations can be exploited as a powerful synthetic tool to construct a variety of organic molecules.



Scheme 60 Electrochemical synthesis of picryl phosphonate



Scheme 61 Oxidation – nucleophilic addition – elimination of proton

8 Electrochemical Version of the S_N^H Reactions

Electrochemical S_N^H reactions have a number of advantages in comparison with chemical routes, such as atom economy, a low cost, ambient temperature and pressure, and high yields of the S_N^H products [49, 79, 164, 182]. This environmentally friendly approach has been successfully applied to cyanation, amination, alkylation, and other S_N^H reactions of nitroaromatic compounds [182–186]. The features of electrochemical S_N^H reactions are discussed in detail in [217], prepared by the Spanish chemists I. Gallardo and G. Guirado.

One of the features of application of electrochemical methods in organic chemistry is that electrochemical synthesis can be carried out under controlled potential, enabling one to oxidize intermediate σ^H-adducts and, at the same time, to avoid oxidation of nucleophilic species.

Electrochemical oxidation of the anionic σ^H-complexes derived from the reaction of 1,3,5-trinitrobenzene with phosphorus nucleophiles proved to be an effective way to the corresponding S_N^H products. For instance, the reaction of TNB with dimethyl phosphonate takes place easily in DMF at room temperature in the presence of potassium *tert*-butoxide under argon atmosphere to give the target dimethyl (2,4,6-trinitrophenyl) phosphonate in 80% yield (Scheme 60) [164].

Besides that, electrochemical methods can be used to activate aromatic substrates by means of "redox–umpolung" procedure, which makes possible to convert unreactive arenes, azoles, phenols, and other aromatic compounds, bearing electron-donating groups, into the intermediate radical cation species, which are able to react with nucleophiles (Scheme 61) [47, 187].

Anodic oxidation allows the replacement of a hydrogen atom for a nucleophile to be fulfilled (Scheme 61), which in non-electrochemical reactions is not possible in one step. This approach to C–H functionalization of arenes appears to be a very promising one, since it meets to the requirements of green chemistry [47, 187].

9 Mechanistic Aspects of the S_N^H Reactions

The S_N^H reactions are often accompanied by the formation of radical species due to a single electron transfer (SET) between an electron-rich nucleophile and electron-deficient substrate.

9.1 Electron Transfer Complexes Between Reactants

The aminoarylation of 9-methylacridinium salts with aromatic amines provides a well-established example of a SET from arylamines to the acridinium ion, as evidenced by the formation of diacridanyl and arylamine radical cation species (Scheme 62). Also, treatment of *N*-methylacridinium ion with *N*,*N*′-tetramethyl-*para*-phenylenediamine, as the model compound, gave the characteristic color of the "Wurster's Blue" radical cation [11, 136, 137].

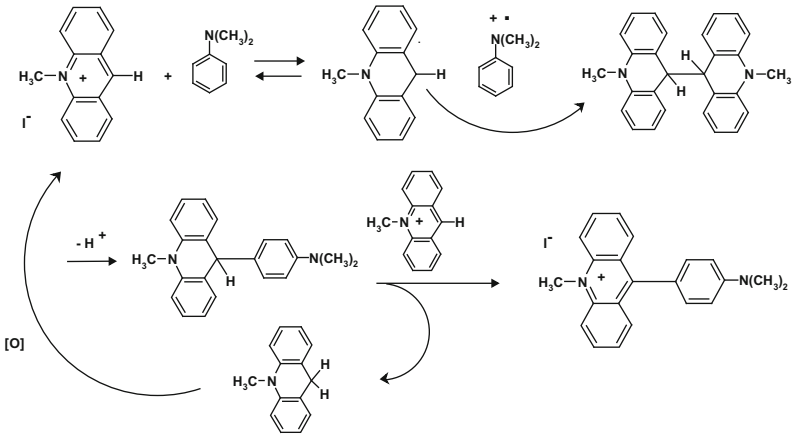
Also the radical species are easily formed on treatment of 1-ethyl-2,3-dicyano-1,4-diazinium [188, 189] and 1-ethyl-1,2,4-triazinium salts [190] with nucleophiles, as evidenced by dimerization of pyrazinyl radicals into the corresponding dimeric structure (Scheme 63). It is worth noting that the synthetic potential of the intermediate radicals can be used as "trapped" with compounds bearing C–C double or triple bonds, for instance by reacting with allyl carboranes. The latter reaction is accompanied by the hydrolysis of one cyano group and results in the formation of the corresponding 2,5-diazabicyclo[2,2,2]octenes (Scheme 63) [189].

9.2 Formation of Intermediate σ^H-Adducts

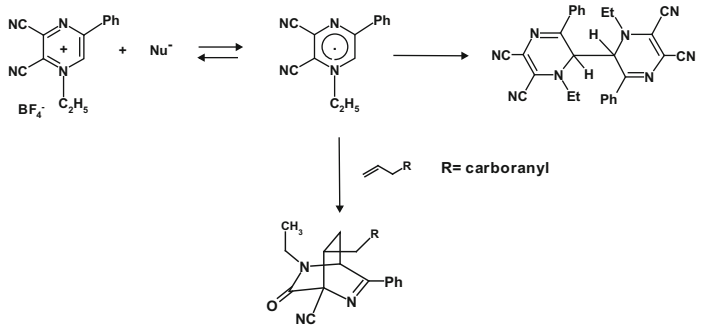
The role of σ^H-adducts in the S_N^H reactions can hardly be overestimated. In fact they are the core structures, determining routes of the S_N^H reactions and other transformations initiated by the formation of σ^H-adducts [1–3, 5, 10–48, 114].

9.2.1 Spectroscopic Evidence for the Formation of σ^H-Adducts

Analytical methods such as UV-visible, IR, and especially NMR spectroscopy are of great importance for both detection of the σ^H-adducts and elucidation of their structure [1–3, 5, 10–48, 114]. In particular, the NMR technique has proved to be a very successful tool for detecting σ^H-adducts due to the fact that in case of their formation both ^1H and ^{13}C resonance signals in the NMR spectra undergo pronounced upfield shifts relative to those for the parent compounds. A considerable body of NMR spectral data has been accumulated in the literature for both anionic



Scheme 62 Electron transfer in aminoarylation of *N*-methylacridinium ion

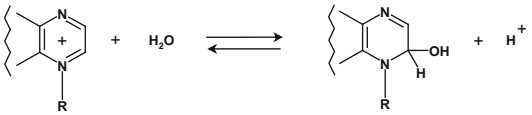


Scheme 63 SET-initiated conversions of 1-ethyl pyrazinium salts

and neutral σ^H-adducts derived from nucleophilic reactions of pyridines, quinolines and isoquinolines [2, 11, 191–193], acridines [11, 136, 137, 192], pyrimidines [11, 88, 192, 193], pyrazines and quinoxalines [2, 11, 114, 163, 170, 194], naphthyridines [195], 1,2,4-triazines [114–117, 170], 1,2,4,5-tetrazines [193, 196], pteridines [114, 170, 197], and other azaaromatic compounds [2, 11, 21, 45].

The tendency of 1,4-diazinium cations to interact with the hydroxide ion has been described in quantitative terms by pK_R+ values, which characterize the equilibrium and give some indication about stabilities of the hydroxy adducts (Table 1). The variation of pK_R+ values in the series of *N*-alkyl-1,4-diazinium cations show that stabilities of the hydroxy σ^H-adducts increase in the following cases: (1) electron-withdrawing substituents are present in the pyrazine ring, (2) benzo annelation, and (3) introduction of the aza group. Indeed, the pyrazinium

Table 1 Values of pK_R+ for a number of 1,4-diazinium cations



K_R+ = [Hydroxy adduct][H^+]/[1,4-diazinium ion][H_2O]

pK_R+ = −log K_R+

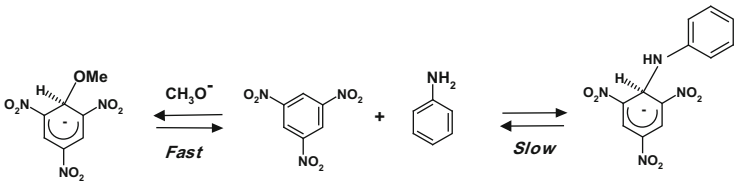
N-Alkyl-1,4-diazinium ion	pK_R+
1-Methylpyrazinium	–
1-Ethylpyrazinium	–
3-Aminocarbonyl-1-methylpyrazinium	8.04
3-Ethoxycarbony-1-methylpyrazinium	6.37
2,3-Dimethoxycarbonyl-1-ethylpyrazinium	3.22
1-Methylquinoxalinium	8.62
1-Ethylquinoxalinium	9.26
1-Methylbenzo[*g*]quinoxalinium	5.73
1-Ethylbenzo[*g*]quinoxalinium	6.32
4-Methyl-6-piperidinopyrido[2,3-*b*]pyrazinium	12.50
8-Ethyl-4-morpholinopteridinium	5.00
8-Ethyl-2-methylthio-4-morpholinopteridinium	7.01
8-Ethyl-2-morpholino-4-methylpteridinium	6.74
8-Ethyl-2-piperidino-4-methylpteridinium	7.63

ion bearing two methoxycarbonyl groups, benzo[*g*]quinoxalinium and pyridinium salts proved to give rather stable hydroxy adducts. In contrast, no indications for adduct formation have been found in the reactions of *N*-alkylpyrazinium and 1,2,4-triazinium salts with the hydroxide ion, and consequently pK_R+ values could not be obtained (Table 1) [170].

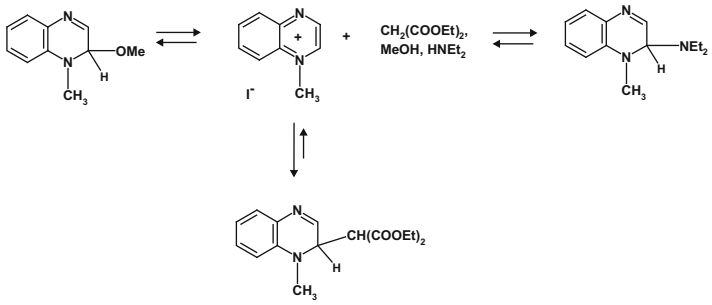
Also the reactions of nitroaromatic compounds with various nucleophiles have been established to give anionic σ^H-adducts, as evidenced from NMR spectra, providing a good diagnostic basis for elucidation of their structure, stability, and chemical transformations. Reactivity of nitroarenes, rate, and equilibrium constants for the formation of anionic σ^H-adducts, as well as the features of the σ^H-adducts, have been discussed in detail in a number of reviews, monographs [1, 2, 5, 10, 11, 15–18, 198], and original papers, for instance [199], dedicated to mechanistic aspects of VNS of hydrogen (for more details [213]).

It is quite common for the S_N^H reactions that at the addition step several nucleophiles are involved concurrently in addition and dissociation reactions. For instance, the reaction of trinitrobenzene with aniline in methanol yields first the methoxy O-adduct which is transformed slowly into the corresponding anilide N-adduct (Scheme 64) [6, 11, 200].

Similar conversions of σ^H-adducts have been observed in the series of 1,4-diazinium salts. For instance, the reaction of *N*-methylquinoxalinium ion with diethyl malonate in methanol in the presence of diethylamine results in the formation of the kinetically favored O- and N-adducts, which are gradually converted into the thermodynamically more stable C-adduct (Scheme 65) [11, 114].



Scheme 64 Concurrently formed O- and N-adducts of trinitrobenzene



Scheme 65 Conversions of O-, N-, and C-adducts of *N*-methylquinoxalinium ion

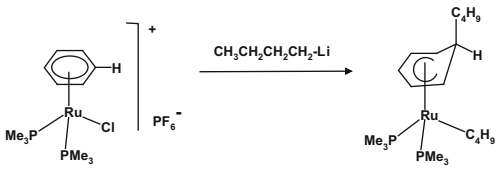
9.2.2 X-Ray Data

Unequivocal evidence for the formation of σ^H-adducts has been obtained by X-ray diffraction analysis of those adducts which are stable enough to obtain their single crystals [11]. Indeed, the X-ray crystallography data are available for the anionic trinitrobenzene-methoxide and the Janovsky trinitrobenzene–acetone complexes [11, 201, 202] and for the σ^H-adducts of isoquinoline [203], phthalazine [160], and 4,7-phenanthroline [161, 162] with dialkyl phosphonates. Also the X-ray data have been obtained for the neutral σ^H-adducts resulting from the reactions of *N*-methylacridinium ion with N-nucleophiles [204, 205] and for the σ^H-adducts of *N*-alkyl-substituted 2,3-dicyanopyrazinium and quinoxalinium salts with O-, C- and P-nucleophiles [163, 194].

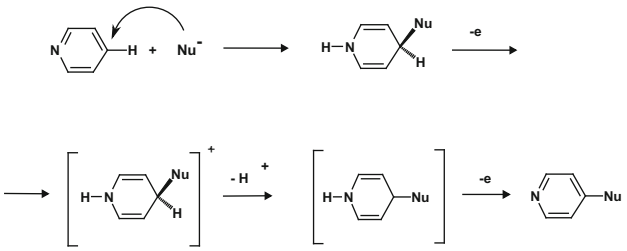
The structural X-ray elucidation of the σ^H-adduct derived from the reaction of benzeneruthenium(II) complex with *n*-butyllithium has revealed that the cyclohexadienyl ring possesses an envelope conformation, in which the *n*-butyl group occupies the exo-position at the sp^3-carbon atom (Scheme 66) [11, 206].

9.3 Oxidation of Intermediate σ^H-Adducts

A great deal of experimental data indicate that the most plausible mechanism of the oxidative step of the S_N^H reactions involves transfer of a single electron from σ^H-



Scheme 66 The σ^H-adduct of benzeneruthenium(II) with *n*-butyllithium



Scheme 67 The most plausible EPE mechanism for oxidation of σ^H-adducts

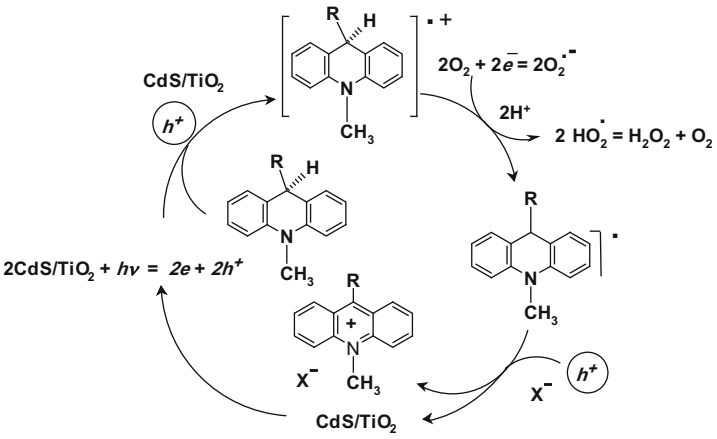
adducts followed by departure of proton and one more electron (Scheme 67) [44]. The stepwise mechanism involving successive electron–proton–electron (EPE) transfer has been substantiated by both electrochemical and chemical experiments. Besides that, there are other oxidative sequences for transfer of proton and two electrons from σ^H-adducts, such as electron–electron–proton (EEP) and proton–electron–electron (PEE) [11, 44].

Due to the nature of electron transfer process, the reaction conditions and rates for oxidative transformations of σ^H-adducts can be improved considerably, provided an appropriate catalyst has been found.

Earlier it was shown that aminoarylation of the *N*-methylacridinium ion by action of *N*,*N*-dialkylanilines proved to proceed on heating of reactants in DMFA, DMSO (120–130°C), or BuOH (105–110°C) in the presence of air bubbling through the reaction mixture (Scheme 62) [136, 137].

Electron transfer processes, kinetics, and mechanisms for the oxidation of 10-methyl-9,10-dihydroacridine, as the model compound, and other 9-substituted 1-methyl-9,10-dihydroacridines have been the subject of many studies [44, 207–211]. In particular, it has recently been found in our laboratory that nanocrystalline TiO_2 with CdS nanoparticles embedded in its pores can accelerate the C–H functionalization of azaaromatic compounds. Indeed, the CdS/TiO_2 composite proved to be an effective visible-light-driven photocatalyst for the oxidative step of the reaction of *N*-alkylacridinium salts with arylamines (Scheme 68).

Thanks to this photocatalyst the S_N^H reaction can be performed in CH_3CN at room temperature in the presence of air oxygen and a catalytic amount of TiO_2 or CdS/TiO_2, provided the reaction mixture is irradiated with a daylight lamp. Also, it is worth noting that oxidation of intermediate dihydroacridines proceeds only in the presence of mineral acids, since the latter are involved into the catalytic oxidative



Scheme 68 A plausible catalytic cycle for oxidation of dihydroacridines

cycle (Scheme 68), as proton donors for oxygen anion radicals. The first elementary steps, which involve the sunlight excitation of a catalytic particle and electron transfer between dihydroacridine and nanoparticles of CdS/TiO_2, are supposed to play the key role to initiate this oxidative process leading to the corresponding radical cation. A plausible catalytic cycle is shown in Scheme 68.

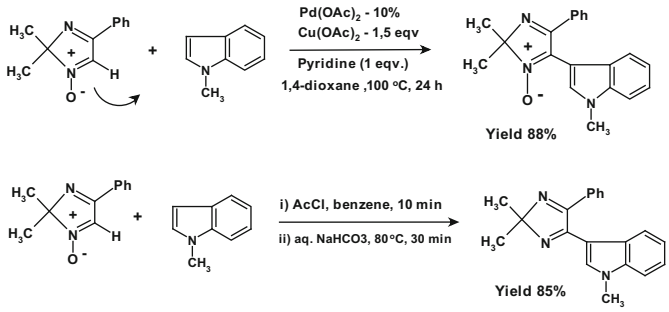
10 Concluding Remarks

It has already been mentioned in Sect. 3 of this chapter that nucleophilic modification of C–H bonds can be realized through either metal activation of C–H bonds or by means of nucleophilic attack at unsubstituted carbon of activated aromatic ring (Scheme 7).

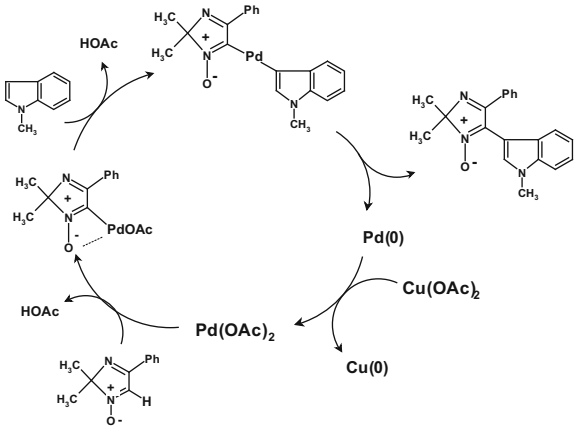
The difference between metal-catalyzed and metal-free C–H/C–H coupling reactions is nicely illustrated by new approaches to modify the structure of imidazolines which have recently been developed in our laboratory (Scheme 69) [212].

The first reaction is catalyzed by palladium acetate. It takes place in the presence of pyridine, as a base, and copper acetate, as oxidant, thus resulting in indolyl-substituted imidazoles with the retention of the *N*-oxide moiety (Scheme 70) [212].

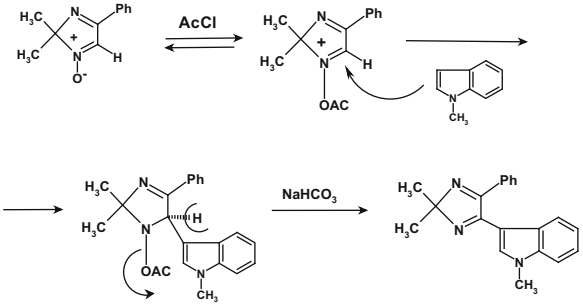
The second reaction is free of metal catalysis. It takes place in the presence of acetyl chloride, proceeds faster, and results in compounds which have the same core structure of indolyl imidazoles, but with the loss of the *N*-oxide group The imidazole ring is activated for a nucleophilic attack by acylation of the *N*-oxide function, and the reaction proceeds according to addition–elimination protocol (Scheme 71) [212].



Scheme 69 Palladium-catalyzed and metal-free C–H/C–H cross-couplings of imidazole *N*-oxides with indoles



Scheme 70 Palladium-catalyzed reaction of imidazole *N*-oxides with indoles



Scheme 71 Metal-free nucleophilic substitution of hydrogen

These and many other examples show a growing interest in both metal-catalyzed and metal-free C–H functionalizations of aromatic and heteroaromatic compounds. However, as mentioned in Sect. 3 of this chapter, this metal-catalyzed reactions are beyond our consideration in this book which focuses on direct nucleophilic attack on unsubstituted carbon of an activated aromatic ring.

It should be noted that the S_N^H methodology and related reactions is a rapidly developing area of organic chemistry. The data of numerous studies obtained by many research groups demonstrate that the S_N^H reactions are not unlikely, but similar to the basic S_EAr processes, they reflect a fundamental nature of aromatic systems [1, 2, 10–18, 45]. The S_N^H reactions provide chemists with facile routes to new carbon–carbon C(sp^2)–C(sp^3), C(sp^2)–C^2), and C(sp^2)–C(sp) bonds, as well as C(sp^2)–O, C(sp^2)–N, C(sp^2)–P, C(sp^2)–S, and C(sp^2)–Hal, i.e., those chemical bonds, the formation of which have earlier been associated with electrophilic aromatic substitution reactions. We believe that the S_N^H methodology, as a powerful synthetic tool, which will be especially useful in the future, since the role of coal, as a raw material, will be a higher, and effective methods for chemical transformations of pyridine bases are expected to be in a great demand.

Finally, we hope that the concept of the S_N^H reactions discussed in this chapter, as well the data of the international team of authors presented in this THC volume, give a convincing evidence for a considerable and growing synthetic potential of the S_N^H reactions and show their value as “chlorine-free” ecologically benign processes.

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Nucleophilic Substitution of Hydrogen in Arenes and Heteroarenes

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Abstract After a short presentation of major variants of nucleophilic substitution of hydrogen, application of these reactions to introduction of substituents into aromatic and heteroaromatic rings and construction of heterocyclic systems are discussed.

Keywords Alkyl hydroperoxides · Amination · Ammonia · Benzimidazole · Benzisoxazole · Carbanions · Heterocycles · Hydroxylation · Indole · Nitro compounds · Nucleophiles · Nucleophilic substitution · Oxidation · Phenazine · Potassium permanganate · Pyridine · Quinoline · Sulfones · Vicarious

Contents

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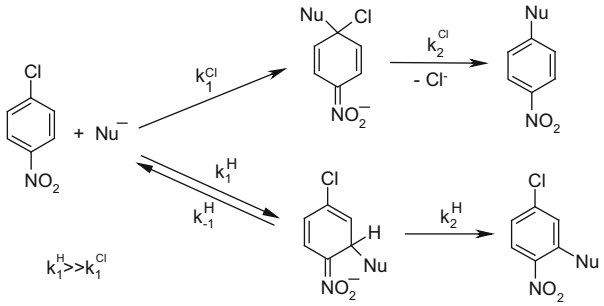
1 Introduction

Nucleophilic substitution of hydrogen in electron-deficient arenes is presently a well-established process proceeding in a few ways [1–5]. Although these reactions are of general character and great practical value for organic synthesis, particularly of heterocyclic systems, they have not been adequately recognized. The key step of these reactions is a fast and reversible addition of nucleophiles to the electron-deficient aromatic rings in positions occupied by hydrogen to form the so-called σ^H adducts. It should be stressed that when the electron-deficient rings contain halogens or other nucleofugal groups X in similarly activated positions, addition of nucleophilic agents in these positions, to form σ^X adducts, proceeds slower than formation of σ^H adducts. The relation of rates is shown in Scheme 1.



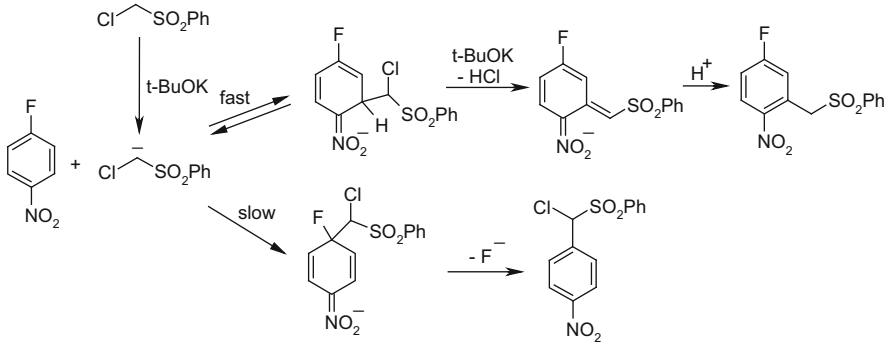
Scheme 1

The initially formed σ^H adducts can be converted into products of nucleophilic substitution of hydrogen in a variety of ways: oxidation with external oxidants, conversion into nitrosoarenes according to intramolecular redox stoichiometry, vicarious substitution, *cine*- and *tele*-elimination, ANRORC, etc. These processes have been discussed in a concise way in our preceding reviews [4, 6–10]. The major message of those reviews is that nucleophilic substitution of hydrogen, in its many variants, is the main, primary process, whereas the conventional nucleophilic substitution of halogens X, the S_NAr process, is just a secondary "ipso" reaction [9, 10].

Here we intend to present a more detailed discussion of the three major ways of conversion of the σ^H adducts into the corresponding products of nucleophilic substitution of hydrogen in nitroarenes, particularly in electron-deficient heterocyclic systems, namely: vicarious nucleophilic substitution (VNS), oxidative nucleophilic substitution (ONSH), and conversion into nitrosoarenes according to intramolecular redox stoichiometry. Our main goal is to show that these reactions offer wide possibilities for the synthesis and modifications of heterocycles.

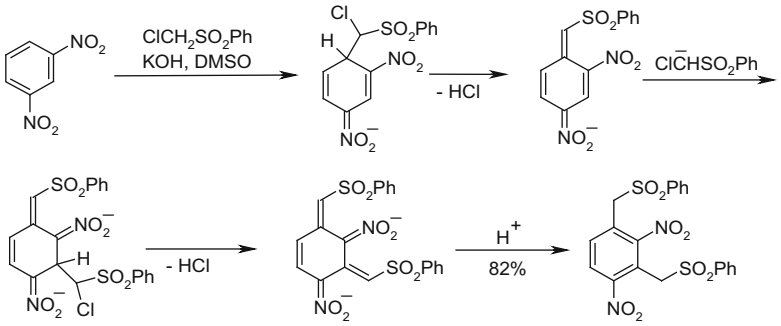
2 Vicarious Nucleophilic Substitution of Hydrogen

Amongst many variants of conversion of the σ^H adducts into the corresponding S_NH products, the vicarious nucleophilic substitution is undoubtedly considered as one of the most versatile and practically important processes [4, 6]. It proceeds when nucleophiles contain nucleofugal groups L at the nucleophilic centers, as, for instance, in the case of α-halocarbanions. Addition of α-halocarbanions to nitroarenes in the *ortho*- or *para*-positions occupied by hydrogen results in the formation of σ^H adducts, which undergo base-induced β-elimination of HL to produce nitrobenzylic carbanions of the S_NH products, isolated upon protonation. Since α-halocarbanions generated from substituted α-chloroalkanenitriles, carboxylic esters, etc. are rather unstable, the carbanion of chloromethyl phenyl sulfone has been chosen as the model nucleophile for investigation of the VNS reactions. Indeed, in the presence of a strong base, this carbanion reacts with nitrobenzene bearing a variety of substituents to replace hydrogen in the *ortho*- and (or) *para*-positions relative to the nitro group. The products, *ortho*- (or *para*-) nitrobenzyl phenyl sulfones, exist in the reaction media in the form of nitrobenzylic carbanions, which are not electrophilic anymore thus, the reaction proceeds exclusively as monosubstitution. It was shown that *ortho*- and *para*-halonitrobenzenes react with this carbanion according to the VNS pathway, resulting in displacement of hydrogen, without competing substitution of halogen (S_NAr reaction). This can be exemplified by selective displacement of 2-hydrogen in 4-fluoronitrobenzene by action of chloromethyl phenyl sulfone under basic conditions (Scheme 2) [11, 12].



Scheme 2

However, under the conditions that favor dissociation of the σ^H adducts and disfavor β-elimination, namely, a higher temperature and absence of a strong base, the conventional S_NAr of fluorine atom can be observed [13]. Interestingly, the reaction of *meta*-dinitrobenzene with an excess of this carbanion gave the disubstitution product, whereas with equimolar amounts of reactants only monosubstitution proceeds. It is evident that the anion of 2,4-dinitrobenzyl phenyl sulfone is still sufficiently active electrophile to react with the carbanion of chloromethyl phenyl sulfone (Scheme 3) [14].



Scheme 3

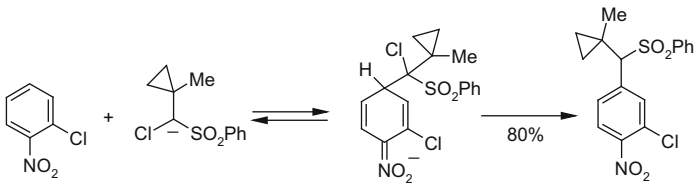
It was subsequently shown that carbanions generated from substituted α-chloroalkanenitriles [15] and alkyl α-chloroalkanoates [16, 17], chloroalkyl oxazolines [18, 19], chloroform [20], etc., although they are much less stable than the model sulfone carbanion, are able to react with nitroarenes to give the VNS products.

2.1 Mechanism

When analyzing plausible mechanisms of the VNS reactions of nitroarenes with α-chlorocarbanions, one should clarify a few key questions: how to proceed the addition and subsequent conversion of σ^H adducts and how other substituents may affect both of these steps – rate and orientation of the addition, rate of the elimination, etc. It is well known that nitroarenes are active electron acceptors, whereas carbanions are good electron donors; thus, these reactants can enter a single-electron transfer (SET) to form anion radicals of nitroarenes and radicals from carbanions [21, 22]. Further coupling of these electrophilic radicals with nucleophilic anion-radical species could give σ^H adducts. This SET pathway, alternative to the direct addition, is often favored by authors and the concept is sometimes abused, see [23] and rebuttal [24]. Nevertheless, numerous observations contradict participation of the SET mechanism in the VNS reactions:

– Orientation of a nucleophile at the addition step can be efficiently controlled by the reaction conditions – namely, addition of the potassium salts of carbanions in DMF and DMSO proceeds in *para*- and *ortho*-positions, whereas in THF it occurs preferentially at the *ortho*-position to the nitro group, because a carbanion in the form of a tight ion pair with K^+ cation is attracted to the *ortho*-position due to interaction of K^+ with oxygen of the nitro group [25]. Such attraction could not operate in case of non-charged radicals, eventually produced from the carbanions via the SET mechanism.

– The σ^H adducts of α-halocarbanions with nitroarenes can be detected by ^1H NMR [26]. The ^1H NMR spectra of a vast majority of σ^H adducts are well resolved and unambiguously interpreted, thus indicating that the formation of paramagnetic species via the SET mechanism is scarcely possible.
– The most straightforward differentiation between the formation of σ^H adducts via two-step SET process and direct nucleophilic addition has been made by using the so-called "fast radical clock". It has been shown that the carbanion of chloro(1-methylcyclopropyl)methyl phenyl sulfone reacts with nitroarenes along the VNS pathway without any complications (Scheme 4), whereas the ring opening rearrangement of the corresponding radical, generated separately, has been shown to proceed with a very high rate constant ~10^9 [27].



Scheme 4

The way of conversion of the σ^H adducts into the VNS products was clarified by taking into account the effects of strength and concentration of base on the rate of the reaction and also by measuring the kinetic isotope effect (KIE) of the reaction. Many observations have indicated that the rate of VNS is affected by the base concentration – mainly on the basis of intramolecular competition between VNS and S_NAr of fluorine, as it has been observed, for instance, for *para*-fluoronitrobenzene (Scheme 2) [13]. For detailed studies of the competition between replacement of 2-F and 6-H, 2-F and 6-D, and 2-H and 6-D, respectively, 2-fluoro-4-bromo-nitrobenzene was chosen as the model compound (Scheme 5). These studies have revealed that k_H/k_F is a function of base concentration at low base concentrations whereas it appears to be constant at high base concentrations [28, 29]. Thus, at a low base concentration the dissociation of σ^H adducts does occur faster than the base-induced β-elimination, the system equilibrates, and the β-elimination is the rate-limiting step. On the other hand, at a high base concentration the σ^H adducts, once formed, undergo a fast β-elimination. Therefore, it is the addition that becomes the rate-limiting step and the k_H/k_F observed is equal to the ratio of the addition rates. These observations and conclusions are also in agreement with the value of k_H/k_D. KIE at low base concentrations proved to be ~4, whereas at high base concentrations the secondary KIE equal to ~0.9 was observed. The significant value of the primary KIE confirms that the second step, the base-induced β-elimination, is the rate-determining one, whereas the secondary KIE shows that the nucleophilic addition associated with sp^2 to sp^3 rehybridization of the carbon atom appears to be the rate-determining step at high base concentrations [29]. Thus, subtle features of the mechanism of VNS were clarified. Also it should

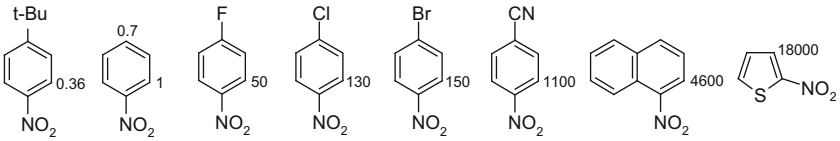
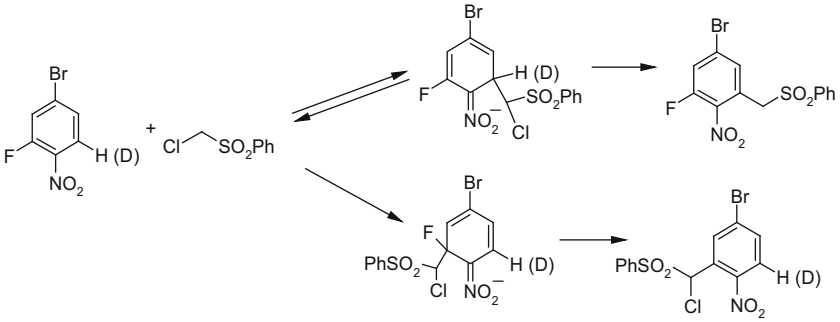


Fig. 1

be mentioned that σ^H adducts were observed by UV–VIS spectroscopy, which enabled to monitor the formation of the σ^H adducts in the reaction mixtures and their conversion into nitrobenzylic carbanions, the final VNS products [26].

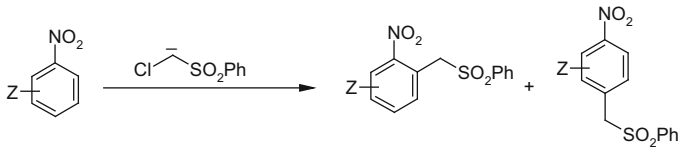


Scheme 5

The effect of substituents on the rate of addition of carbanions to nitroarenes and the rate of β-elimination of HL from the σ^H adducts have also been studied [8, 30, 31]. The former effect is an important parameter, because it is, in fact, a measure of influence of substituents on electrophilic activity of nitroaromatic rings. The effect of substituents on rate of the S_NAr reactions of *o*- and *p*-halonitrobenzenes has been thoroughly studied [2, 32]. However, since the S_NAr of halogen is a secondary process, the obtained data cannot be used as a real measure of electrophilicity of halonitroarenes. We have determined the effects of substituents and the ring structure on the rate of the VNS reaction of nitroarenes with the carbanion of chloromethyl phenyl sulfone by using competitive experiments under the conditions, which assure a fast β-elimination of HL from the σ^H adducts [30, 31]. The values of VNS rates obtained under such conditions proved to correlate with those of the addition step. Selected values of the relative rate constants in relation to nitrobenzene as the standard are shown in Fig. 1.

The VNS reactions always proceed in the *ortho*- or/and *para*-positions relative to the nitro group. When both of these positions are available for a nucleophilic attack, the ratio of *ortho*-/*para*-substitution is determined by the nature of carbanion and the reaction conditions. Less sterically demanding, secondary carbanions can react in both of these positions, whereas bulky tertiary carbanions react preferentially in the *para*-position to the nitro group. It has been however

shown that even tertiary carbanions react preferentially in the *ortho*-positions under the kinetically controlled conditions, namely, at low temperatures and with a high concentration of a strong base [33]. On the other hand, it is the *para*-substitution pattern that dominates under thermodynamic control at higher temperature and low concentration of a weak base [30]. Several examples of the formation of kinetic and thermodynamic products depending on the reaction conditions are shown in Scheme 6.



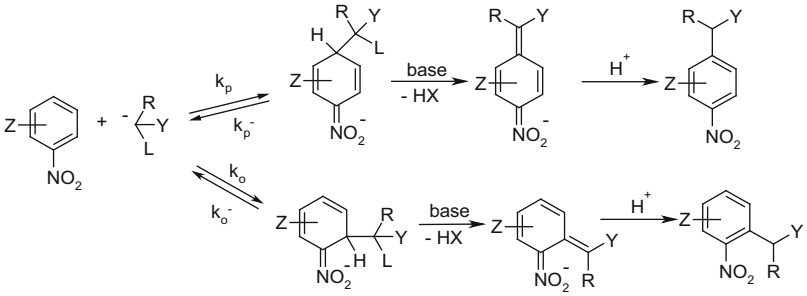
Z = H,	kin	74	26
	ther	0	100
Z = 4-F,	kin	100	0
	ther	0	100*
Z= 3-Cl,	kin	85	15
	ther	0	100

*product of S_NAr of fluorine

Scheme 6

2.2 Scope of the Reaction

The VNS in nitroarenes with carbanions is presented in general in Scheme 7, thus, discussion of the scope and limitations of this reaction should clarify what kind of carbanions (nature of Y, L, and R) and nitroarenes (kind of Z) can enter the reaction.

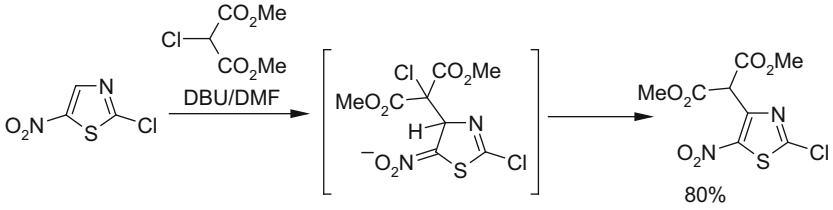


Scheme 7

From the very mechanism it stems that L in the carbanions should be a nucleofugal group, which is able to be eliminated from the σ^H adducts as HL. Besides halogen atoms (Cl, Br), alkoxy, aryloxy, alkylthio, and arylthio groups and many other substituents can be eliminated in this way. There are practically no limitations concerning substituents R and groups Y, stabilizing the carbanions.

Thus, the VNS is of wide scope, as far as carbanions are concerned. Similarly, the reaction has no restrictions in respect of substituents Z in the nitroaromatic ring, which might be halogens, alkoxyl, aryl, and any functional group. In fact, it is sufficient for the nitroarene ring to have at least one position, *ortho*- or *para*-, to the nitro group, which is occupied by hydrogen atom – and this hydrogen can be replaced with a functionalized carbon substituent via VNS. Only substituents that under highly basic reaction conditions are deprotonated into anions directly conjugated with an aromatic ring hinder the VNS reaction, because such rings are not electron-deficient anymore. Indeed, mono-nitrophenols and mono-nitrothiophenols fail to enter VNS reaction; however, dinitrophenols react satisfactorily [14]. This is the reason why the VNS proceeds in mononitroarenes selectively as monosubstitution, whereas dinitroarenes can form products of mono- and disubstitution.

A serious limitation of VNS is connected with its mechanism, namely, conversion of intermediate σ^H adducts into the VNS products via bimolecular base-induced β-elimination. To cause the reaction, it is therefore necessary that these σ^H adducts be produced in a reasonable concentration. Indeed, low nucleophilic carbanions, such as dimethyl chloromalonate, do not react with moderately electrophilic nitrobenzene because of unfavorable equilibrium of the addition step, but react nicely with more electrophilic nitrothiazoles (Scheme 8) [34].

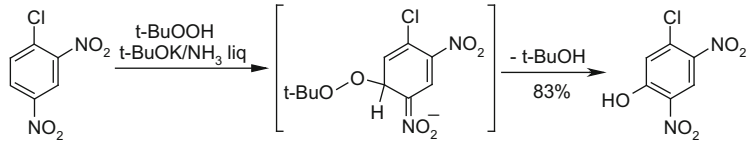


Scheme 8

A plethora of electron-deficient arenes can enter the VNS reaction: carbocyclic and heterocyclic aromatic compounds activated by the nitro group and arenes that are active electrophiles due to their electronic configuration, such as azulene [35, 36], electron-deficient annulenes [37], tropylium cation [38], and particularly azines and azinium cations. Interestingly, η^6-transition metal complexes of arenes, such as benzene tricarbonylchromium, do not enter the VNS reactions. Although the addition of carbanions to these electron-deficient rings proceeds efficiently, and these adducts can be oxidized to form the products of ONSH, the β-elimination of HCl from the σ^H adducts of α-halocarbanions does not occur [39, 40].

Besides carbanions, oxygen and nitrogen nucleophiles containing nucleofugal groups at the O- and N-nucleophilic centers can provide efficient hydroxylation and amination of nitroarenes according to the VNS pathway. Thus, anions of commercially available *tert*-butyl and cumyl hydroperoxides, although being moderately active nucleophiles, are able to add to nitroarenes of sufficient activity to form σ^H adducts. Subsequent base-induced β-elimination of the corresponding alcohols

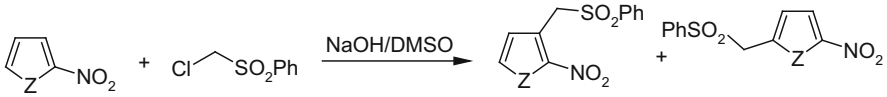
followed by protonation affords *o*- and *p*-nitrophenols [41]. Also in these cases the nucleophilic substitution of hydrogen proceeds faster than the conventional S_NAr of halogen. For instance, anions of both of these hydroperoxides react with 2,4-dinitrochlorobenzene to produce 2,4-dinitro-5-chlorophenol in excellent yield (Scheme 9) [41, 42].



Scheme 9

Amination of nitroarenes with hydroxylamine, known for over 100 years [43], proceeds undoubtedly according to the VNS mechanism. Modern aminating agents, such as 4-amino-1,2,4-triazole [44–46], sulfenamides [47, 48], and *O*-methyl hydroxylamine [49, 50], are more versatile and efficient than hydroxylamine. 1,1,1-Trimethyl hydrazinium iodide proved to be particularly useful for this purpose [51–53]. Amination with this reagent proceeds via addition of the hydrazino moiety followed by a base-induced β-elimination of trimethylamine from the corresponding σ^H adducts.

Nitro derivatives of five-membered heterocycles are active partners in the VNS reactions [54]. It is interesting to compare the results of the VNS reactions with the model carbanion of chloromethyl phenyl sulfone, obtained for the following series of compounds: 2-nitrothiophene, *N*-methyl-2-nitropyrrole, and 2-nitrofuran (Scheme 10) [55]. Although in these 2-nitroheterocycles the position 3 appears to be the preferred addition site, a low yield of the VNS product derived from the reaction of 2-nitrofuran and the formation of 5-isomer from *N*-methyl-2-nitropyrrole requires rationalization [54]. These results indicate that the orientation is affected by conjugation of the electron pairs of these heteroatoms with the nitro group. Indeed, when 2-nitropyrrole was N-protected by phenylsulfonyl group (Z=NSO_2Ph) to prevent such conjugation, the VNS reaction proceeded exclusively in position 3 [55]. The addition to 2-nitrofuran takes place in both 3- and 5-positions; however, decomposition of the σ^H adducts at C-5 via the ring opening appears to proceed faster than β-elimination, thus giving rise to the only product derived from the VNS in the position 3 [54].



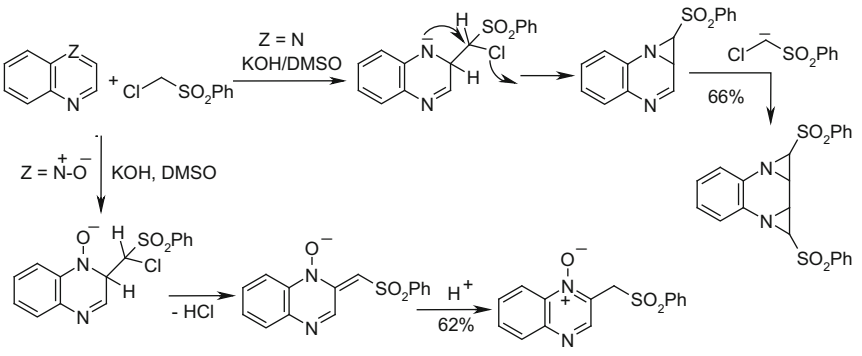
Z = S	74%	-
Z = O	23%	-
Z = N-Me	-	90%
Z = N-SO_2Tol	83%	-

Scheme 10

This reasoning is supported by the observation that the reaction of 2-nitrofuran with trichloromethyl carbanion proceeds in both 3- and 5-positions, because in this case the base-induced β-elimination of HCl from the intermediate σ^H adducts is a fast process [54]. Also the VNS reactions of nitro derivatives of other 5-membered heterocycles, imidazoles [20, 56] and thiazoles [34], with a variety of α-halogeno carbanions have been shown to proceed efficiently.

Pyridine is known to exhibit a significant electron-deficient character, thus being able to add strong nucleophiles, such as alkyl lithium or amide anion. However, its electrophilic activity is not sufficient to add moderately active nucleophiles, such as α-halocarbanions. On the other hand, all isomeric 2-, 3-, and 4-nitropyridines react smoothly with the carbanion of chloromethyl phenyl sulfone [57] and a variety of other α-halocarbanions [58–60], thus giving the expected VNS products. Electrophilic activity of the pyridine ring is strongly enhanced via the formation of pyridinium salts that can be exploited in intramolecular VNS reactions, leading to isothiazolo[4,3-*b*]pyridines [61]. Also *N*-pyridyl dicyanomethylides enter the VNS reaction with a variety of α-halocarbanions [62]. Some azines are active electrophiles per se and do not need activation by electron-withdrawing substituents. A convincing example is 1,2,4-triazine in which all three positions 3, 5, and 6 are vulnerable for a nucleophilic attack. The most active position in the 1,2,4-triazine ring is 5, then 3, and 6 [63, 64].

Some peculiar observations were made when the model carbanion of chloromethyl phenyl sulfone was reacted with quinoxaline (Scheme 11) [65]. Instead of the expected VNS product, the *bis*-aziridine derivative was formed. It was suggested that in the initially formed σ^H adducts the negative charge was mostly located on the vicinal nitrogen atom, thus facilitating the 1,3-intramolecular nucleophilic substitution, leading to mono-aziridine derivative [65]. Addition of the second molecule of the same carbanion to the C=N bond proceeds faster than the first addition to aromatic quinoxaline system, thus giving *bis*-aziridine compound as the final product. This reasoning was substantiated by the reaction of quinoxaline N-oxide with the same model carbanion, proceeding along the VNS pathway, because the negative charge of the σ^H adducts was located mostly on the oxygen atom (Scheme 11) [65].



Scheme 11

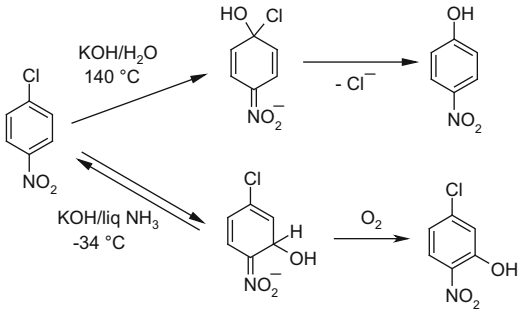
A variety of other azaaromatic compounds, pteridines [66], pyridazines [67] etc., enter the VNS reactions with the model carbanion of chloromethyl phenyl sulfone or other α-chlorocarbanions. In these reactions azine N-oxides are more active electrophiles than azines themselves. For instance, quinoline fails to enter the VNS reaction with the model carbanion, whereas quinoline N-oxide reacts rather smoothly [68]. Also 3-(chloromethylsulfonyl-amino)pyridine-N-oxide and its quinoline analogue are able to undergo intramolecular VNS reactions [61].

3 Oxidative Nucleophilic Substitution of Hydrogen

Since hydride anions are unable to depart spontaneously from the anionic σ^H adducts, they should be removed by external oxidants. However, possibilities for conversions of the σ^H adducts into products of oxidative nucleophilic substitution of hydrogen (ONSH) appear to be limited, since nucleophiles, and particularly carbanions, are usually sensitive to oxidation. Thus, ONSH can be feasible in two major cases:

a. Nucleophiles are resistant toward oxidation.
b. Addition of nucleophiles to electron-deficient rings, affording σ^H adducts, proceeds to completion.

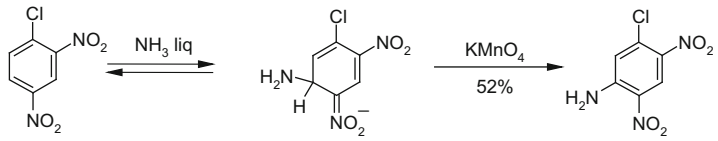
Indeed, ONSH proceeds efficiently with nucleophiles resistant toward oxidation, such as hydroxide anion and ammonia. Many textbooks on organic chemistry describe the "hydrolysis" of *para*-chloronitrobenzene on heating with aqueous KOH, which in fact is the S_NAr reaction, proceeding via intermediacy of σ^{Cl} adducts. However, when this nitroarene is exposed to KOH and oxygen at low temperature in liquid ammonia, 2-nitro-5-chlorophenol is formed in high yield (Scheme 12) [69].



Scheme 12

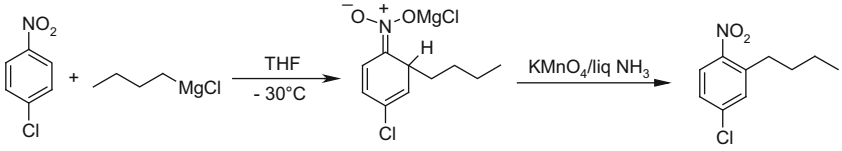
Thus, it is evident that σ^H adducts with the hydroxide anion are formed much faster than isomeric σ^{Cl} adducts, and at low temperature these species are long-lived enough to be oxidized by oxygen. A similar situation appears to occur in the reaction

of halonitroarenes with ammonia. Since $KMnO_4$ is well soluble in liquid ammonia, such solution can be used for oxidative amination. The system $KMnO_4$/liquid ammonia proved to be a very useful tool for amination of electron-deficient heterocycles – the procedure, which is often termed as oxidative version of the Chichibabin reaction [70]. Also it has been unambiguously shown that ONSH is faster than the conventional S_NAr of halogen, as illustrated in Scheme 13 [71].



Scheme 13

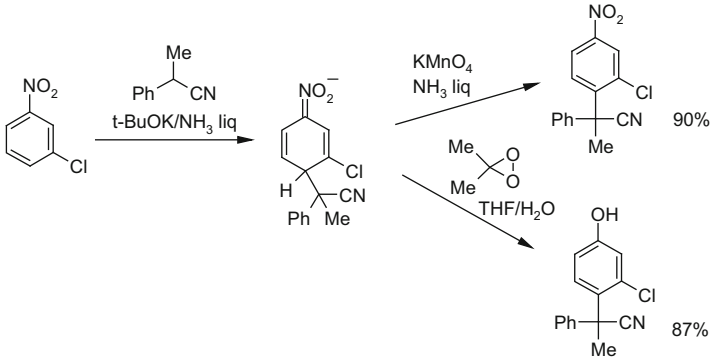
There are two major variants of ONSH with nucleophiles sensitive to oxidation: (a) addition is an irreversible process; and (b) equilibrium of the reversible addition is shifted in favor of the σ^H adducts. Nucleophilic organometallic compounds, alkyllithium and alkyl-magnesium reagents, are active enough to add irreversibly to nitroarenes in positions occupied by hydrogen to form the σ^H adducts [72]. Due to irreversibility of the addition, the S_NAr reaction on treatment of *ortho*- and *para*-halonitrobenzenes with these C-nucleophiles is not observed. Further oxidation of the formed σ^H adducts with a variety of oxidants, preferably $KMnO_4$, affords products of oxidative nucleophilic alkylation. This reaction appears to be an important method for direct incorporation of alkyl substituents into aromatic rings (Scheme 14) [72, 73].



Scheme 14

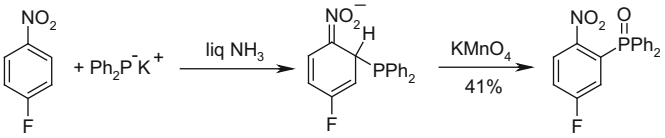
Equilibrium of the addition of nucleophiles to nitroarenes is a function of many factors, such as their nucleophilicity, electron deficiency of arenes, and their ability to stabilize σ^H adducts, as well as the reaction conditions. Thus, all these parameters are responsible for the feasibility of ONSH with nucleophiles sensitive to oxidation. Of substantial importance is temperature, since, due to the entropy factor, the equilibrium is shifted toward the adducts at a low temperature. For instance, addition of highly nucleophilic carbanion of 2-phenylpropionitrile to moderately active *m*-chloro nitrobenzene at −70°C in liquid ammonia or DMF/THF proceeds to completion, selectively in the *para*-position. Further oxidation of the formed σ^H adducts with

$KMnO_4$ in liquid ammonia, or with dimethyldioxirane in THF, gave 2-phenyl-2-(*para*-nitrophenyl)- and 2-phenyl-2-(*para*-hydroxyphenyl)-propionitriles, respectively (Scheme 15) [74, 75].



Scheme 15

The effect of temperature on the addition equilibrium can, for instance, be observed in the reaction of the carbanion of diethyl benzylphosphonate with 4-fluoronitrobenzene. At low temperature the addition proceeds exclusively at the position 2, and oxidation of the produced σ^H adduct affords the product of ONSH. On the other hand, at room or a higher temperature the S_NAr of fluorine in the position 4 takes place [76]. Similarly, when the reaction of nitroarenes with the anion of diphenylphosphine is carried out at low temperature in liquid ammonia in the presence of $KMnO_4$ diphenyl(nitroaryl)phosphine oxides are formed, as illustrated by the ONSH in 4-fluoronitrobenzene (Scheme 16) [77].



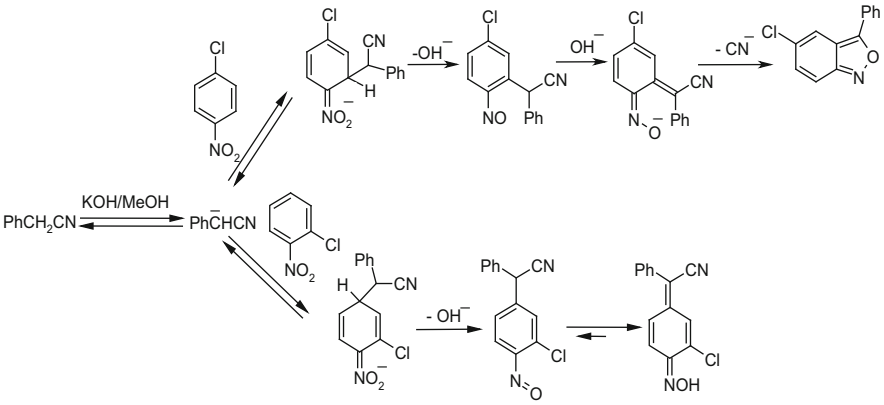
Scheme 16

The σ^H adducts of nitroarenes with various nucleophiles can be oxidized with a few oxidants, and oxygen is probably the most common oxidant, although it has a limited application. It oxidizes σ^H adducts resulted from the addition of OH^- anion to nitroarenes to produce nitrophenols and also σ^H adducts of secondary and primary carbanions. Some observations and experiments lead to conclusion that for oxidation by oxygen the anionic σ^H adducts should first be deprotonated, so in fact, dianions are oxidized [78]. Oxidation of such σ^H adducts with oxygen appears to proceed via an electron transfer. On the other hand, oxidation of the σ^H adducts of nitroarenes with ammonia, the Grignard reagents, various carbanions, or diphenylphosphine by action of $KMnO_4$ appears to proceed via direct abstraction of the

hydride anion, as is suggested by high value of the kinetic isotope effect of the oxidation [79]. Oxidation of such σ^H adducts with dichlorodicyanoquinone (DDQ) also appears to proceed via abstraction of the hydride anions.

4 Conversion of σ^H Adducts into Nitrosoarenes

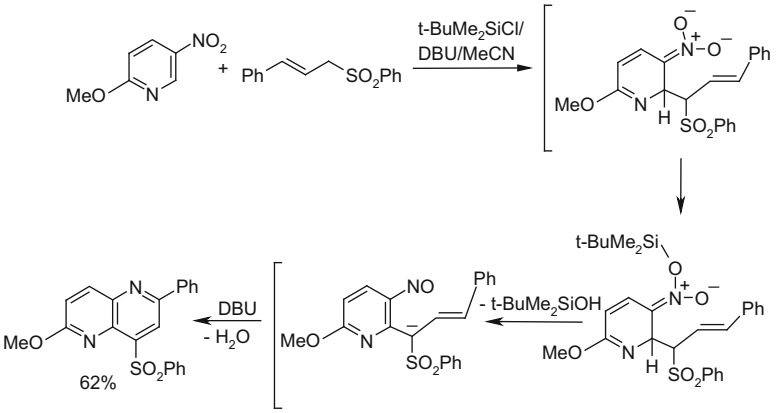
The third general way of converting the σ^H adducts of nucleophiles to nitroarenes involves elimination of water or other small molecules to form substituted nitrosoarenes, according to intramolecular redox stoichiometry. For example, phenylacetonitrile and other arylacetonitriles react with nitroarenes in the presence of KOH in protic media to form nitrosoarenes or products of their further transformations (Scheme 17) [80, 81].



Scheme 17

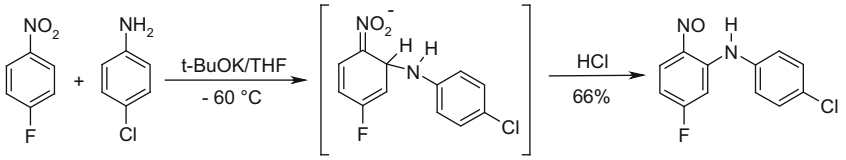
It appears that the reaction proceeds via protonation of the intermediate anionic σ^H adducts followed by elimination of water to form nitrosoarenes. Since nitrosoarenes are very active electrophiles, they can undergo further transformations by action of nucleophilic agents and usually are not isolated as such. However, when conversion of σ^H adducts is carried out as a separate step without base and nucleophiles, the substituted nitrosoarenes might be isolated, often in good yields. Due to high activity of the nitroso group in inter- and intramolecular reactions, this way of conversion of σ^H adducts becomes a versatile tool for organic synthesis, in particular for obtaining of heterocycles. For instance, treatment of a mixture of 3-phenylallyl phenyl sulfone and 6-methoxy-3-nitropyridine with DBU and *t*-butyldimethylsilyl chloride results in the formation of substituted naphthyridine (Scheme 18) [82]. The reaction proceeds via addition of the sulfone carbanion

followed by conversion of the intermediate σ^H adducts into nitrosoarene and subsequent intramolecular condensation of the newly generated ambident carbanion with the formed nitroso group.



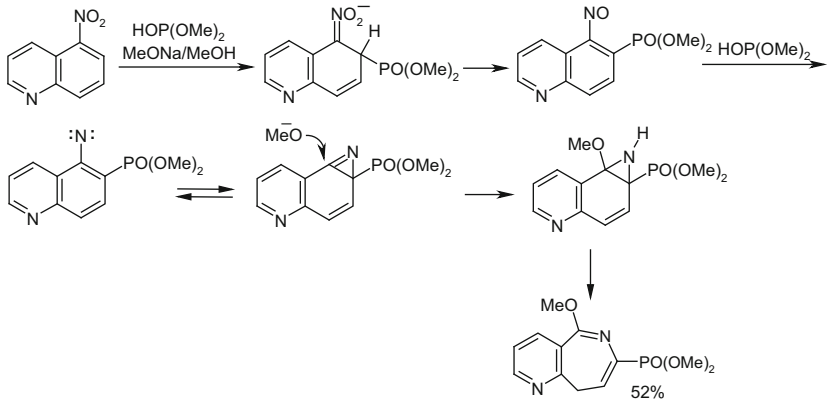
Scheme 18

Reactions of nitroarenes with anilines in the presence of a strong base, proceeding via intermediacy of the corresponding σ^H adducts (Scheme 19), are of particular interest since they provide a synthetic way to valuable 2-nitrosodiarylamines [83–86]. Thus, when *p*-chloro- or *p*-fluoronitrobenzene was reacted with anilines in the presence of *t*-BuOK in THF at low temperature (−60°C), 2-nitroso-5-chloro (or fluoro)phenyl arylamines were obtained in good yields (Scheme 19) [85]. Competing S_NAr of halogen was not observed under these conditions. It should be mentioned that a simple mixing of these *p*-halonitrobenzenes with anilines at elevated temperatures results in S_NAr of halogen [87].



Scheme 19

The reaction of 1-nitronaphthalene and other bicyclic nitroarenes, for instance, 5-nitroquinoline, with dimethyl phosphite in methanol in the presence of sodium methoxide proceeds via formation of the corresponding σ^H adducts with the phosphite anion, which are converted into substituted nitrosoarenes. Subsequent N-deoxygenation results in the formation of nitrenes that react further to give benzazepines and analogues (Scheme 20) [88].



Scheme 20

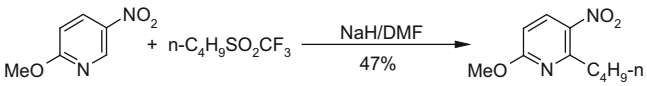
5 Introduction of Substituents into Electron-Deficient Heterocycles via Nucleophilic Substitution of Hydrogen

In the following sections we will present some recent examples of introduction of various substituents into heteroarenes via nucleophilic substitution of hydrogen. The full account of the previous results was given in our preceding reviews [4, 89, 90].

5.1 Carbon Substituents

The introduction of carbon substituents into electron-deficient aromatic and heteroaromatic rings is of great importance because products can be of interest per se and can also serve as valuable intermediates in further synthesis, particularly in heterocyclizations.

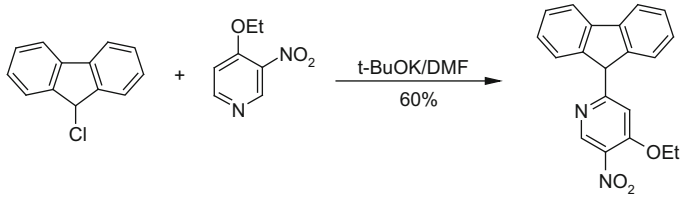
Alkyl substituents can be incorporated directly into nitroheteroaromatic rings via the VNS reactions with carbanions of alkyl trifluoromethyl sulfones (Scheme 21) [91].



Scheme 21

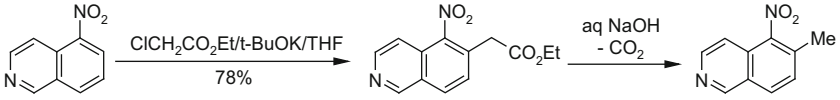
Diarylmethylation of nitroarenes can be performed efficiently via VNS, using carbanions of benzhydryl aryl sulfides [92]. Similarly, the VNS reaction of 4-ethoxy-3-nitropyridine with carbanion of 9-chlorofluorene results in incorporation of the

fluorenyl fragment into the pyridine ring (Scheme 22) [93]. Also heteroarylmethyl substituents were introduced into nitroarenes via the VNS reactions with carbanions of chloromethyl derivatives of pyridine, thiazole, and benzothiazole [94].



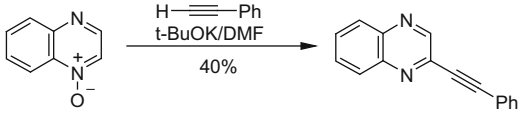
Scheme 22

Alkyl substituents can be introduced into heterocyclic rings also via direct ONSH reaction with the Grignard reagents [72] or via the VNS reaction with carbanions of α-chloroalkyl carboxylic esters [17], followed by hydrolysis and decarboxylation [95–97]. For example, treatment of 5-nitroisoquinoline with the carbanion of ethyl chloroacetate under the standard VNS condition in DMF in the presence of t-BuOK gave the expected (5-nitroisoquinol-6-yl)acetate, which was transformed into 6-methyl-5-nitroisoquinoline via hydrolysis and decarboxylation (Scheme 23) [95].



Scheme 23

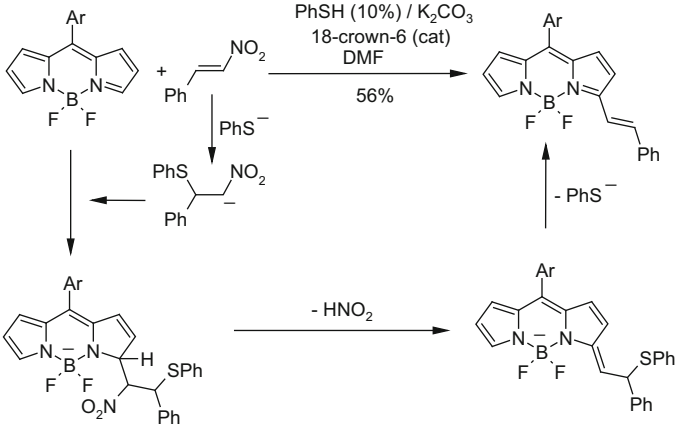
Synthesis of a variety of phenylethynylazines can be performed by using the methodology of direct nucleophilic replacement of hydrogen in the reactions of azine N-oxides with the carbanion of phenylacetylene (Scheme 24) [98].



Scheme 24

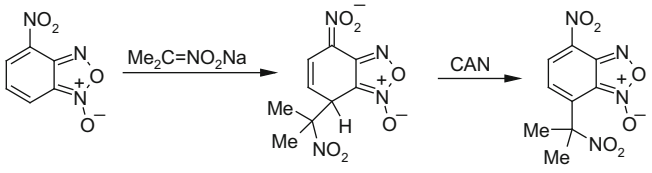
An exceptional example of introduction of alkenyl substituent via nucleophilic substitution of hydrogen is phenylethenylation of boron-dipyrromethene (BODIPY), which has been realized in the reaction of the latter with *β*-nitrostyrene

catalyzed by the phenylthiolate anion (Scheme 25) [99]. The initial step of the reaction is the Michael-type addition of thiolate to nitrostyrene to form the nitronate anion which adds to the electron-deficient pyrrole ring, followed by base-induced elimination of nitrous acid. In the final step, elimination of the thiolate results in incorporation of phenylvinyl substituent and regeneration of the catalyst.



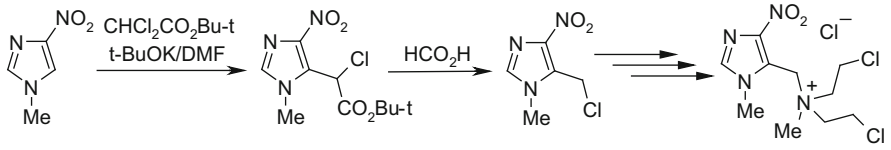
Scheme 25

Even weak C-nucleophiles, such as 2-nitropropenide anion, are able to add quantitatively to superelectrophilic nitrobenzofurazan and nitrobenzofuroxan. Further oxidation of the intermediate σ^H adducts with ammonium cerium(IV) nitrate (CAN) results in incorporation of α-nitroisopropyl substituent into these heterocyclic systems (Scheme 26) [100].



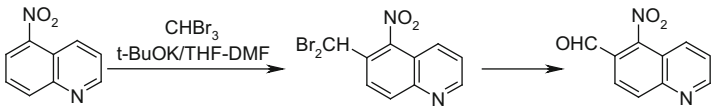
Scheme 26

We have described a two-step method for introduction of chloromethyl substituents into nitroarenes. This approach consists in the VNS of hydrogen with *tert*-butyl dichloroacetate anion [58] followed by one-pot hydrolysis and decarboxylation [101]. This approach has been used for the synthesis of (chloromethyl) nitroimidazole, a precursor of (nitroheteroaryl)methyl mustard, which was tested as hypoxia-selective cytotoxins (Scheme 27) [102].



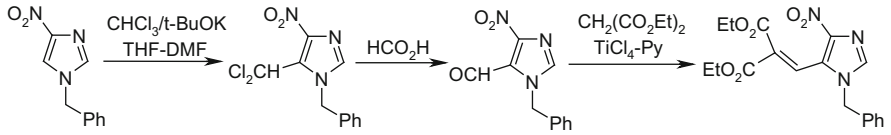
Scheme 27

On the other hand, direct dihalomethylation of electron-deficient arenes via VNS with trihalomethyl carbanions generated by deprotonation of haloforms is a general process [20]. Due to facile hydrolysis of the dihalomethyl group, the reaction can be considered as nucleophilic formylation. This approach has already found wide application in the synthesis of heterocyclic aldehydes, which are difficult to obtain by other methods [103–105]. For example, the VNS reaction of 5-nitroquinoline with tribromomethyl carbanion affords 6-(dibromomethyl)-5-nitroquinoline, which is transformed by hydrolysis into the corresponding aldehyde, the starting material for the synthesis of biologically active coumarin derivative (Scheme 28) [103].



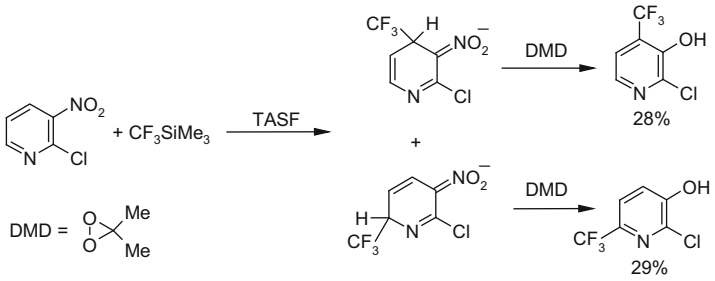
Scheme 28

The VNS of hydrogen in 1-benzyl-4-nitroimidazole by action of trichloromethyl carbanion results in the formation of 5-dichloromethyl derivative (Scheme 29). Hydrolysis and condensation of the resulting aldehyde with diethyl malonate afford the corresponding alkene that, upon reduction of the nitro group, undergoes cyclization into imidazopyridone [106].



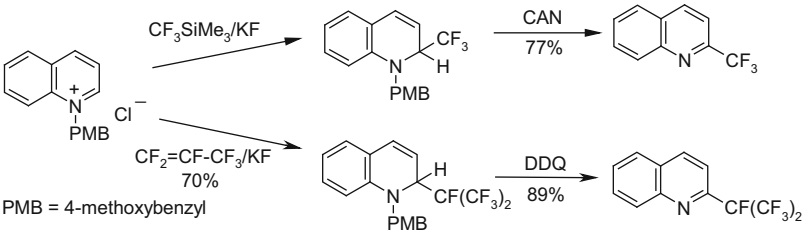
Scheme 29

The synthesis of fluoroalkyl-substituted heterocycles is a subject of continuous interest; this challenging issue has been presented in details in reviews [107, 108]. It has been shown that trifluoromethyl carbanion, generated from (trifluoromethyl) trimethylsilane (the Ruppert reagent), adds easily to 2-chloro-3-nitropyridine. The produced σ^H adducts can be oxidized with dimethyldioxirane (DMD) to form two isomeric 2-chloro-4-(and 6-)trifluoromethyl-3-hydroxypyridines (Scheme 30) [109].



Scheme 30

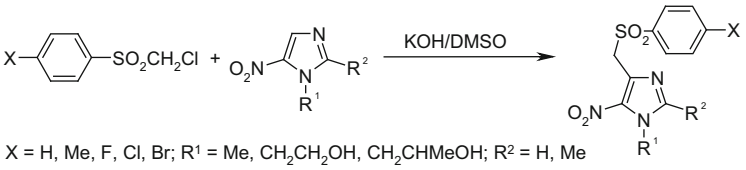
Similarly produced trifluoromethyl carbanion, as well as perfluoroisopropyl carbanion generated by addition of fluoride anion to perfluoropropene, is able to add to a variety of *N*-(4-methoxy-benzyl) pyridinium and quinolinium salts. The obtained dihydroazines can easily be transformed into 2-perfluoroalkyl azines through oxidative dealkylation–aromatization with CAN or DDQ (Scheme 31) [110, 111].



Scheme 31

The VNS is the reaction of choice for incorporation of α-sulfonylalkyl substituents into nitroarenes and their heteroanalogues. Particularly accessible and useful are nitroarylmethyl phenyl sulfones and their heteroanalogues that are efficiently produced in the VNS reactions of carbanions of chloromethyl aryl sulfones with a great variety of nitroarenes and nitroheteroarenes. Nitro derivatives of heterocycles, such as pyrrole [54, 55], furan [54], thiophene [54], imidazole [106, 112, 113], pyrazole [114], pyridine [57], indole [115], indazole [116, 117], benzimidazole [118], benzotriazole [119], benzofuroxan [120], quinoline [121], and porphyrins [122, 123], have been shown to enter this reaction.

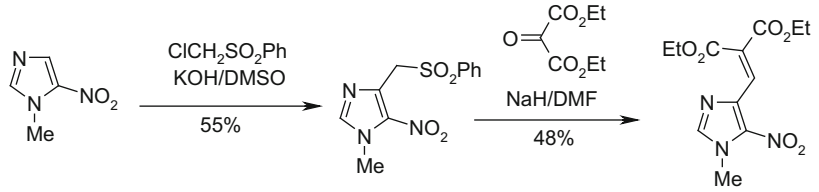
In search for new antiparasitic agents active against *Trichomonas vaginalis*, a number of 4-(arylsulfonylmethyl)-5-nitroimidazole derivatives have been prepared via the VNS reaction of 4-nitroimidazoles with substituted aryl chloromethyl sulfones (Scheme 32) [124].



X = H, Me, F, Cl, Br; R^1 = Me, CH_2CH_2OH, $CH_2CHMeOH$; R^2 = H, Me

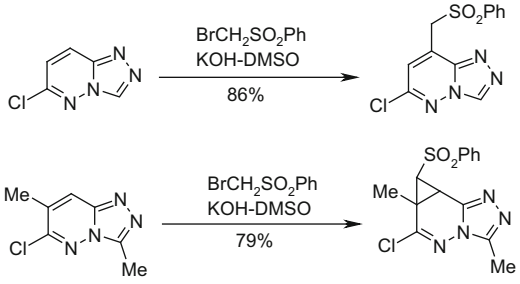
Scheme 32

Introduction of arylsulfonylmethyl substituents into nitroheteroaromatic rings is of great practical value because these sulfones are versatile intermediates in organic synthesis. Nitrobenzyl aryl sulfones and their heterocyclic analogues can easily be transformed into the corresponding ethenyl derivatives by a simple alkylation with simultaneous elimination of arylsulfinate anion [125]. Diethyl methylenemalonate substituent can be introduced in the position 4- of 5-nitroimidazole via the VNS reaction of 5-nitroimidazole with the carbanion of chloromethyl phenyl sulfone [112, 124], followed by condensation of the obtained 4-(phenylsulfonyl)methyl derivative with diethyl bromomalonate or diethyl ketomalonate (Scheme 33) [126].



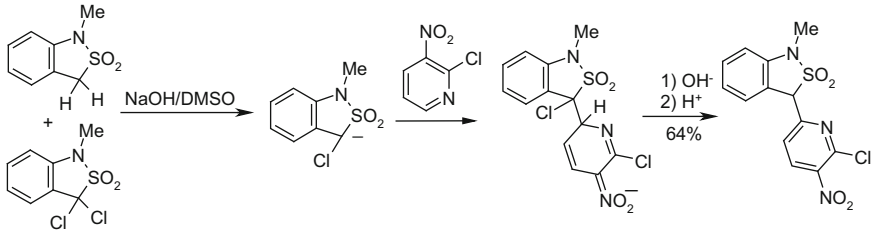
Scheme 33

Azolopyridazines bearing no nitro substituent are, nevertheless, sufficiently active electrophiles to enter the VNS reaction. However, similar to the series of quinoxalines [127] and pyridazinones [67], in the reactions of azolopyridazines with the carbanion of bromomethyl phenyl sulfone, two ways for conversion of the intermediate σ^H adducts are observed, depending on the structure of these heterocyclic compounds – β-elimination, leading to the VNS product, or intramolecular substitution, resulting in formation of the cyclopropane ring (Scheme 34) [128].



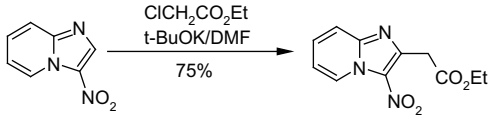
Scheme 34

The monochlorobenzosultam carbanion, generated through symproportionation of an equimolar mixture of benzosultam and its dichloro derivative, is capable of addition to 2-chloro-3-nitropyridine. Subsequent elimination of HCl from the intermediate σ^H adduct affords 3-(pyridin-2-yl)-substituted benzosultam according to the VNS mechanism (Scheme 35) [129].



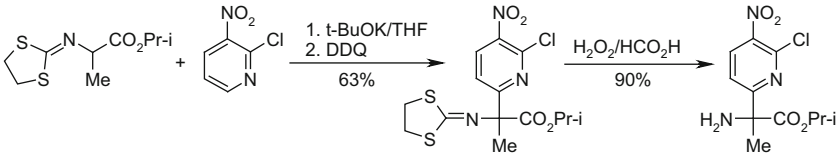
Scheme 35

3-Nitroimidazo[1,2-*a*]pyridine reacts smoothly with the carbanion of ethyl chloroacetate to give the expected VNS product bearing ethoxycarbonylmethyl substituent at position 2 (Scheme 36) [130].



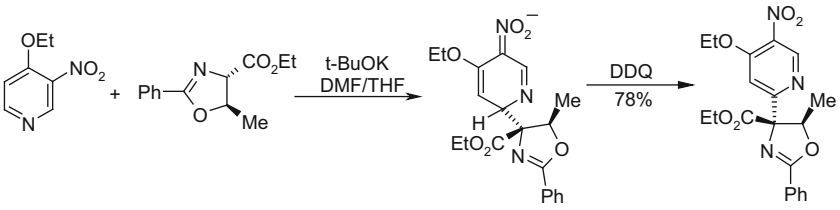
Scheme 36

Oxidative nucleophilic substitution of hydrogen in the reactions of nitroarenes with carbanions of protected amino acids offers an access to α-(nitroaryl)amino acids and their heteroanalogues. According to this protocol, nitropyridines react with carbanions of protected alanine, serine, and threonine esters to give the corresponding nitropyridyl α-amino acids [131–133]. For example, *N*-(1,3-dithiolane-2-ylidene)alanine isopropyl ester, which is readily available from the reaction of alanine ester with carbon disulfide and 1,2-dibromoethane, adds to 2-chloro-3-nitropyridine in THF in the presence of t-BuOK to form the σ^H adduct that upon oxidation with DDQ and hydrolysis gives the corresponding ester of α-nitroarylalanine (Scheme 37) [132].



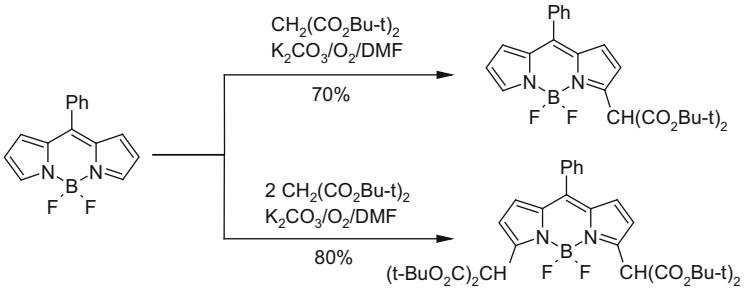
Scheme 37

Also carbanions of serine and threonine esters, protected in the form of oxazolines, are capable of addition to nitropyridines to form the corresponding σ^H adducts that can be oxidized into α-(nitropyridyl) amino acid derivatives [132]. It should be mentioned that addition of the carbanion of the protected threonine to nitropyridine proceeds with a high diastereoselectivity, which is controlled by the second chiral center present in the oxazoline ring (Scheme 38) [133].



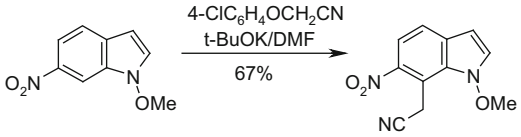
Scheme 38

Under much milder conditions, oxidative substitutions in BODIPY's with malonic esters, acetophenone, and ethyl phenylacetate proved to take place (Scheme 39). For example, the reaction with *tert*-butyl malonate in the presence of potassium carbonate and oxygen proceeds at the position 3. When a twofold excess of nucleophile was used, 3,5-disubstituted product was obtained [134].



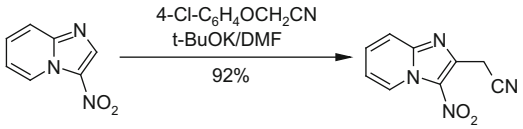
Scheme 39

1-Alkyl-5- and 1-alkyl-6-nitroindoles undergo the VNS substitution of hydrogen at the positions 4 and 7, respectively, by action of chloromethyl sulfones and (4-chlorophenoxy)acetonitrile to give the corresponding VNS products in high yields [115]. 1-Methoxy-6-nitroindole reacts in a similar manner, yielding the expected 7-indolylacetonitrile (Scheme 40) [135].



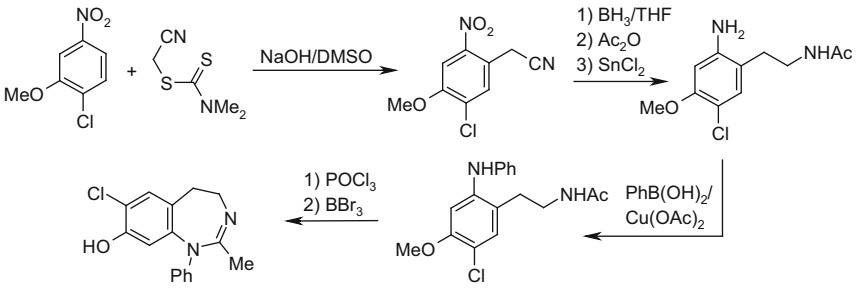
Scheme 40

3-Nitroimidazo[1,2-*a*]pyridine has been reported to react efficiently with carbanion of (4-chlorophenoxy)acetonitrile to give the expected VNS product containing the cyanomethyl group at position 2 (Scheme 41) [130].



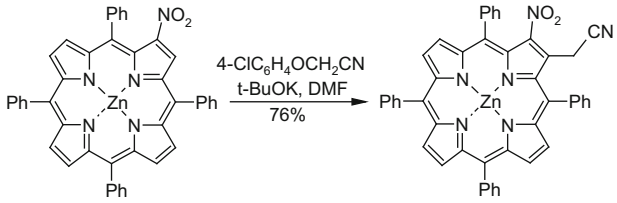
Scheme 41

2-Arylphenylamines required for the synthesis of novel dopamine antagonists, containing the 1,3-benzodiazepine fragment [136], have been prepared from 5-chloro-4-methoxy-2-nitrophenylacetonitrile, derived from the reaction of 2-chloro-5-nitroanisole with cyanomethyl dimethyldithiocarbamate, proceeding via typical VNS procedure (Scheme 42) [15].



Scheme 42

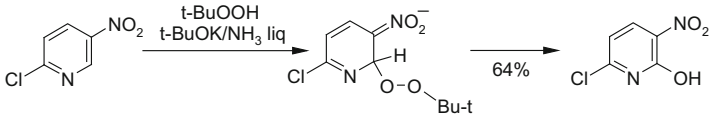
Nitro derivatives of arylporphyrins, which contain the nitro group in the pyrrole rings, enter the VNS reaction with carbanions bearing a leaving group at α-position, thus giving the expected substitution products in good yields (Scheme 43) [123].



Scheme 43

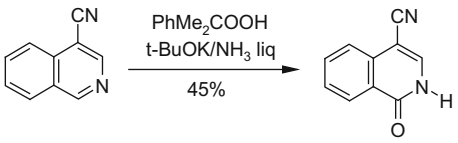
5.2 *Hydroxylation*

Nitro derivatives of a variety of heteroaromatic compounds enter the VNS reactions with alkyl hydroperoxide anions to produce the expected hydroxylation products [41, 137–139]. For instance, the VNS hydroxylation of 2-chloro-5-nitropyridine with *tert*-butylhydroperoxide was shown to give 2-chloro-5-nitro-6-hydroxypyridine that exists in its tautomeric form of pyridone [41] (Scheme 44). It should be stressed that the S_NAr of chlorine located in the highly activated position 2 was not competing with the VNS.



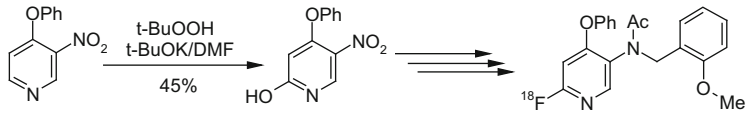
Scheme 44

The addition of nucleophiles to bicyclic heteroaromatic systems usually proceeds more easily; thus, activation of isoquinoline by the cyano group is sufficient for the VNS hydroxylation (Scheme 45) [41].



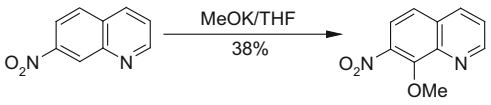
Scheme 45

tert-Butylhydroperoxide was used for the synthesis of 2-hydroxy-4-phenoxy-5-nitropyridine; the latter was subsequently converted into ^{18}F-labeled PBR28 radiotracer (Scheme 46) [138].



Scheme 46

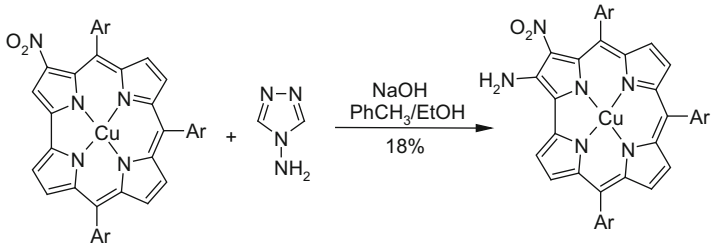
Also nitroquinolines undergo the direct methoxylation with potassium methoxide in THF, as exemplified in Scheme 47 [140].



Scheme 47

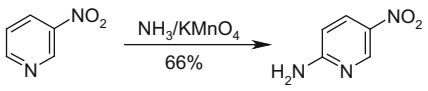
5.3 Amination

The VNS amination requires ammonia derivatives, bearing good leaving groups at nitrogen, as starting materials. Thus, derivatives of hydrazine (trimethylhydrazinium halides and 4-amino-1,2,4-triazole) and hydroxylamine (methoxyamine and arylsulfenamides) proved to be efficient aminating agents. The VNS amination of 3-nitropyridine and its substituted derivatives was observed to proceed efficiently with 4-amino-1,2,4-triazole [46, 60], hydroxylamine [46], and methoxyamine in the presence of zinc chloride [49]. Amination of 5-, 6-, 7-, and 8-nitroquinolines [141, 142], 4-nitroisoquinoline [46], 5- and 6-nitrobenzimidazoles [143], nitro-1,2,3- and nitro-1,2,4-triazoles [144], dinitropyrazole [145], dinitroquinazoline [146], and dinitroindazoles[147] with 1,1,1-trimethylhydrazinium iodide was also reported. Nitrophenyl fragments in porphyrins were aminated successfully with 2,4,6-trichlorophenyl sulfenamide [148, 149]. Triphenylporphyrin derivatives, in which the internal ring is activated by the carbonyl group, were aminated with 4-amino-1,2,4-triazole [150, 151]; similarly nitrocorroles were aminated, as shown in Scheme 48 [152].



Scheme 48

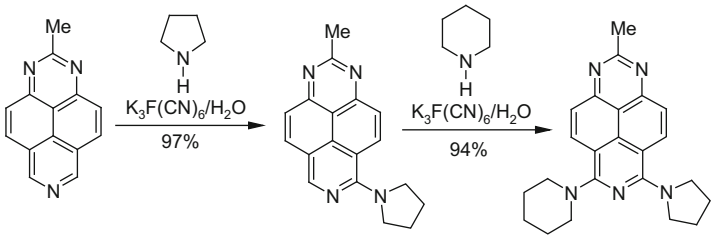
Oxidative amination of 3-nitropyridine with ammonia, alkyl- and dialkylamines, and $KMnO_4$ as oxidant was reported by Bakke (Scheme 49) [60].



Scheme 49

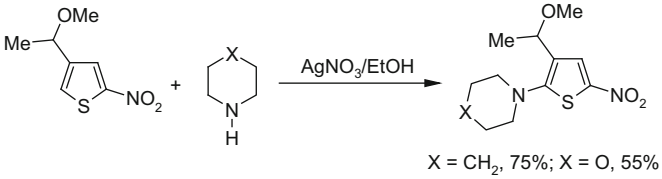
The mechanism of oxidative alkylamination of 3-nitropyridine, quinazoline, and 1,3-dinitrobenzene with permanganate anion, including determination of the kinetic isotope effect for the oxidation step, was thoroughly studied [153]. *Bis*(pyridine) silver(I)permanganate $AgPy_2MnO_4$ [154–156] was found to be superior to $KMnO_4$ for the reaction of higher alkyl and dialkylamines, inter alia, due to a low solubility of $KMnO_4$ in these amines. However, in the presence of tetraalkylammonium chloride, which forms lipophilic tetraalkylammonium permanganate, the latter oxidant becomes equally active [153].

1,3,7-Triazapyrenes were aminated successfully into mono- and bis-dialkylamino compounds under mild conditions in aqueous solution with potassium hexacyanoferrate(III) as oxidant (Scheme 50) [157, 158].



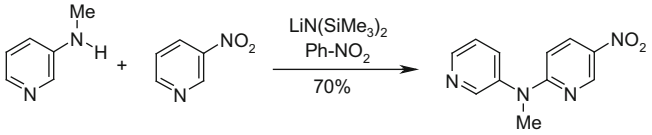
Scheme 50

Aliphatic and cyclic dialkylamino groups can also be incorporated into 4-substituted-2-nitrothiophenes via the ONSH with dialkylamines and $AgNO_3$, as oxidant (Scheme 51) [159].



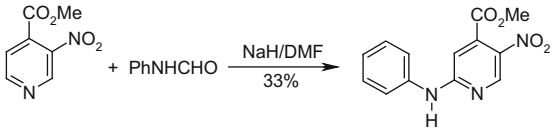
Scheme 51

In oxidative amination of nitropyridines with 2-, 3-, and 4-aminopyridines, leading to *N,N′*-dipyridylamines, nitrobenzene proved to be effective as oxidant (Scheme 52) [160].



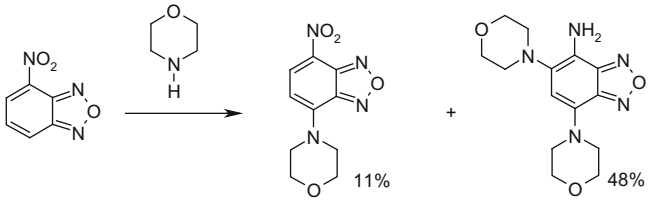
Scheme 52

3-Nitro-1,5-naphthyridines were oxidatively methylaminated in liquid methylamine as solvent in the presence of potassium permanganate [161]. Direct oxidative amination of 3-nitronicotinate with formanilide proceeds at the position 6 of the pyridine ring, resulting in the formation of anilinopyridine (Scheme 53) [162].



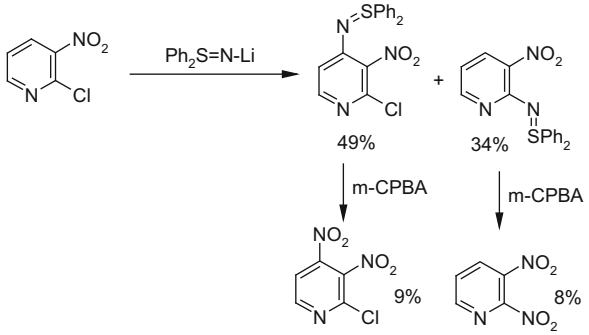
Scheme 53

An unusual reaction course was observed in the reaction of dialkylamines with 4-nitrofurazan [163]. Indeed, treatment of the latter with an excess of morpholine gave two products, one of them being derived from oxidative substitution of hydrogen in position 7, while the second, *bis*-morpholino compound, proved to be the result of the redox process (Scheme 54).



Scheme 54

Oxidative nucleophilic substitution of hydrogen in 2-chloro-3-nitropyridine by action of *N*-lithio-*S*,*S*-diphenylsulfilimines has been shown to be accompanied with the S_NAr displacement of chloro atom (Scheme 55). Both of these products were oxidized with m-CPBA to form dinitropyridines [164, 165].



Scheme 55

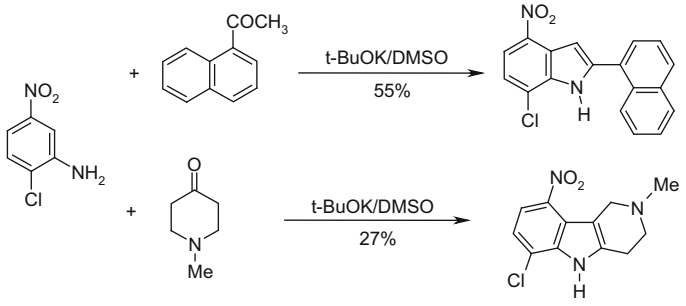
6 Construction of Heterocyclic Compounds via Nucleophilic Substitution of Hydrogen

6.1 Indoles

The indole fragment is present in a great variety of biologically active compounds and other products of practical importance. It is no wonder that use of the reactions aimed at construction of indole skeleton is of significant value. Nucleophilic substitution of hydrogen opens a wide avenue for the synthesis of indoles, bearing a variety of substituents in both aromatic and heteroaromatic rings, as well as for obtaining of azaindoles and indoles condensed with other ring systems.

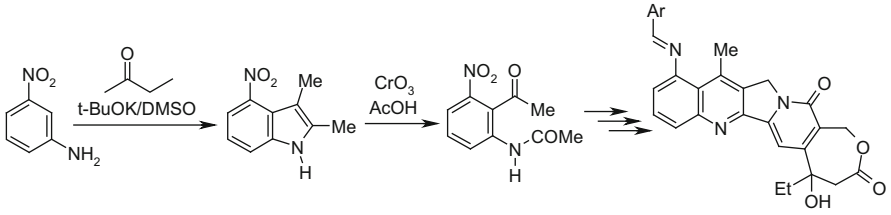
There are two key starting materials for the synthesis of indoles via nucleophilic substitution of hydrogen: *meta*-nitroaniline and its derivatives and nitroarenes or their heterocyclic analogues. In the first case nitrogen of the amino group is the precursor of the indole nitrogen, whereas in case of nitroaromatic compounds it is nitrogen of the nitro group.

The synthesis of 4- and 6-nitroindoles via the direct reaction of *meta*-nitroanilines with ketone enolates appears to be the simplest and the most efficient one in terms of atom economy. This method of the indole moiety construction, exemplified in Scheme 56, is of general character, considering ketones and *meta*-nitroanilines, which might bear a variety of substituents [166, 167]. This approach has enabled the synthesis of all kinds of substituted indole derivatives including cycloalkeno[*b*]indoles, tetrahydrocarbazoles, and tetrahydrocarbolines, when cyclic ketones were employed (Scheme 56) [167]. It should be mentioned that this versatile method can be applied to a large-scale synthesis [168].



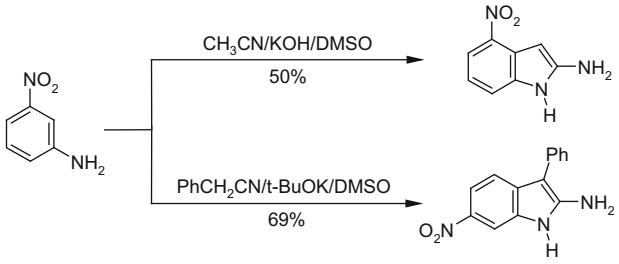
Scheme 56

Despite simplicity and versatility of this new way of indole synthesis, there have been only few reports on application of this reaction to the synthesis of compounds of biological interest [168–170]. Thus, 2,3-dimethyl-4-nitroindole, obtained according to [167], was oxidized to nitroacetophenone derivative, which was used as a starting material for the synthesis of homocamptothecin derivatives, tested as potential inhibitors of DNA topoisomerase I (Scheme 57) [170].



Scheme 57

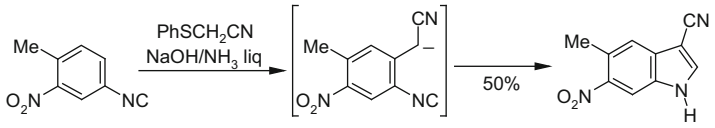
Similar heterocyclizations were shown to proceed between *meta*-nitroanilines and carbanions of alkanenitriles to produce 2-amino-4-(and -6-)nitroindoles. For example, the reaction of *meta*-nitroaniline with acetonitrile leads to 2-amino-4-nitroindole, while 6-nitroindole derivative is formed in the reaction with phenylacetonitrile (Scheme 58) [171].



Scheme 58

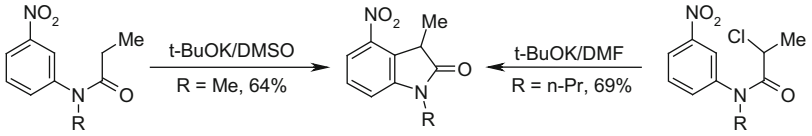
Both reactions proceed via the addition of carbanions to the nitroaromatic ring followed by oxidation of the intermediate σ^H adducts by atmospheric oxygen to form the corresponding nitrobenzyl nitriles, which undergo intramolecular cyclizations.

meta-Nitrobenzoisonitriles can readily be obtained from *meta*-nitroanilines. The VNS reaction of these isonitriles with carbanions of sulfones and nitriles, bearing good leaving groups, leads to *ortho*-isocyanobenzyl sulfones and cyanides, respectively. Under the reaction conditions intramolecular addition of the intermediate carbanions to the isocyano group takes place, resulting in the formation of substituted indoles (Scheme 59) [172].



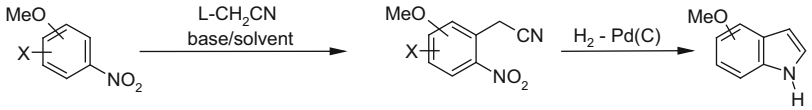
Scheme 59

4-Nitro-2-oxo-2,3-dihydroindole derivatives (nitrooxindoles) can be obtained by intramolecular ONSH [173] and VNS [174] reactions of *meta*-nitroanilides of alkanoic and α-chloroalkanoic acids (Scheme 60).



Scheme 60

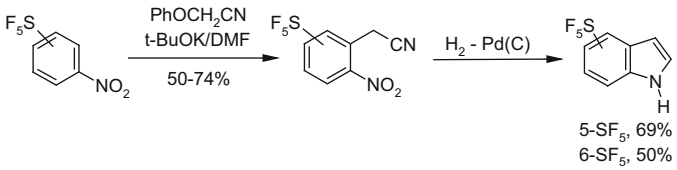
Introduction of functionalized carbon substituents in the *ortho*-position to the nitro group of nitroarenes provides even wider possibilities for the synthesis of indoles. One particularly useful pathway is direct cyanomethylation of nitroarenes with chloroacetonitrile or, more conveniently, aryloxyacetonitriles to produce *ortho*-nitroaryl acetonitriles that can further be converted into indoles in a few ways. It is worth to note that synthesis of indoles via catalytic hydrogenation of such nitriles has been well known for many years [175], however was of a limited value, because *ortho*-nitroaryl acetonitriles were not easily available. Facile synthesis of *ortho*-nitroaryl acetonitriles via the VNS methodology has opened a wide avenue to a variety of substituted indoles. Moreover, some halogen substituents (Cl, Br) in the nitroaromatic rings may not only improve effectiveness of the VNS reactions but also prevent introduction of cyanomethyl substituent into undesired positions [176, 177]. Such auxiliary substituents can be subsequently removed during hydrogenation. The general character and versatility of this approach to indoles is nicely illustrated by the synthesis of all isomeric 4-, 5-, 6-, and 7-methoxy-substituted indoles via the VNS cyanomethylation of isomeric nitroanisoles and their halogenated derivatives (Scheme 61) [176].



X = H, Cl, Br; L = 4-ClC_6H_4O, R_2NCS_2: base - NaOH, t-BuOK; solvent - DMSO, DMF

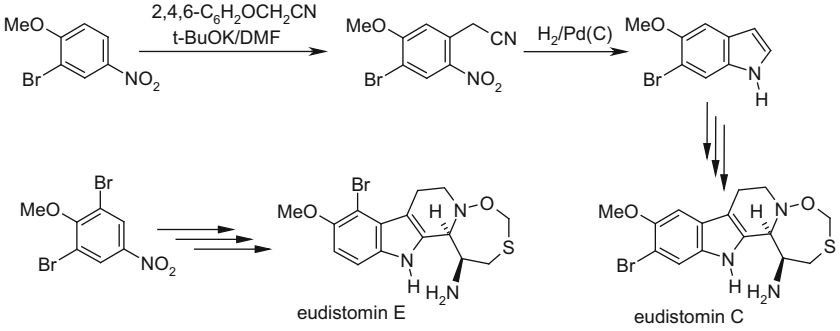
Scheme 61

Similarly, hydroxyindoles can be obtained via the VNS cyanomethylation of benzyl nitrophenyl ethers, eventually containing halogens in nitrophenyl rings followed by hydrogenation and simultaneous removal of the benzyl group and halogens [176, 177]. Recently the VNS cyanomethylation followed by hydrogenation has been used for synthesis of indoles containing pentafluorosulfanyl substituents (Scheme 62) [178].



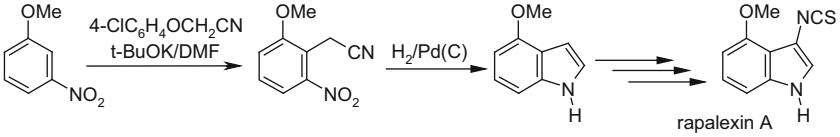
Scheme 62

In the synthesis of eudistomins C and E, antiviral agents of marine origin containing 5-methoxyindole fragment, both indole units were prepared via vicarious nucleophilic substitution with aryloxyacetonitriles (Scheme 63) [179]. A proper choice of both nitroarene and cyanomethylating agent enabled synthesis of the prerequisite nitrophenyl acetonitriles to be performed. 4-Bromo-5-methoxy-2-nitrophenylacetonitrile, required for the synthesis of eudistomin C, was prepared via the VNS cyanomethylation of 2-bromo-4-nitroanisole with 2,4,6-trichlorophenoxyacetonitrile. The bulky leaving group in the carbanion appears to suppress substitution of hydrogen at sterically hindered position 3 in 2-bromo-4-nitroanisole. 6-Bromo-5-methoxyindole was synthesized by hydrogenation of this nitroaryl-substituted acetonitrile and then transformed in a few steps into eudistomin C [179]. A similar strategy has been used in the synthesis of eudistomin E from 2,6-dibromo-4-nitroanisole and 4-chlorophenoxyacetonitrile [179].



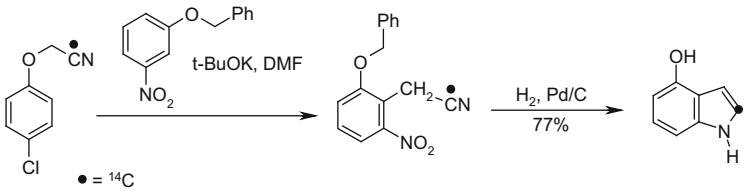
Scheme 63

Interestingly, the VNS reaction of 3-nitroanisole with 4-chlorophenoxyacetonitrile proceeds in the most hindered position 2 [176]. 2-Nitro-6-methoxyphenylacetonitrile obtained was then reduced and converted into 4-methoxyindole, which was then transformed in three steps into rapalexin A, an unusual isothiocyanate alkaloid derived from *Brassica rapa* (Scheme 64) [180].



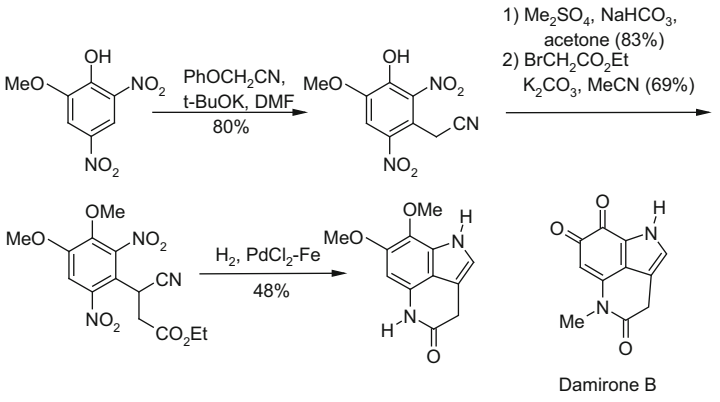
Scheme 64

4-Hydroxyindole, a starting material for the synthesis of β-blockers, can be obtained analogously from 3-benzyloxynitrobenzene [176, 181]. Cyanomethylation of this nitroarene with 4-chlorophenoxyacetonitrile also proceeds at the position 2. Further catalytic hydrogenation of the obtained nitroarylacetonitrile provides 4-hydroxyindole [176]. Similarly, the VNS cyanomethylation of 3-benzyloxynitrobenzene with 4-chlorophenoxyacetonitrile containing ^{14}C in the cyano group was used for the synthesis of 2-^{14}C-labeled 4-hydroxyindole (Scheme 65), an intermediate for the synthesis of a pindolol analogue LY3688242 [182].



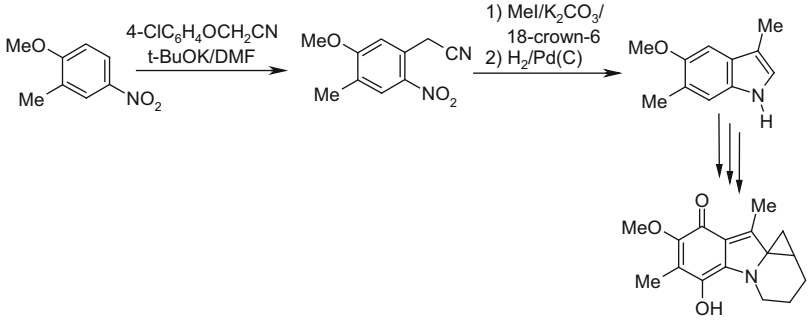
Scheme 65

Ortho-nitroaryl-substituted acetonitriles are relatively strong C–H acids, and their C-alkylation followed by hydrogenation leads to 3-substituted indoles [176]. It has been shown earlier that VNS in 2,4-dinitrophenol proceeds regiospecifically at the most hindered position 3 due to electronic configuration of the dinitrophenolate anion [14]. This orientation pattern has been employed for the synthesis of the precursor of damirone B from dinitroguaiacol, in which cyanomethylation proceeds exclusively at position 5 to form upon *O*-methylation 3,4-dimethoxy-2,6-dinitrophenylacetonitrile. Further alkylation of the nitrile carbanion with ethyl bromoacetate and hydrogenation provides the skeleton of damirone tricyclic system (Scheme 66) [183, 184].



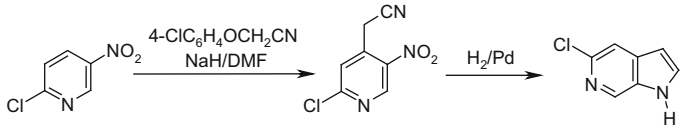
Scheme 66

3,6-Dimethyl-5-methoxyindole prepared via the VNS cyanomethylation of 3-methyl-4-methoxynitrobenzene has been used as starting material for the synthesis of cyclopropano-annelated quinone methide, a reductive alkylating agent for in vitro studies of its interactions with deoxyguanosine-5′-monophosphate (Scheme 67) [185].



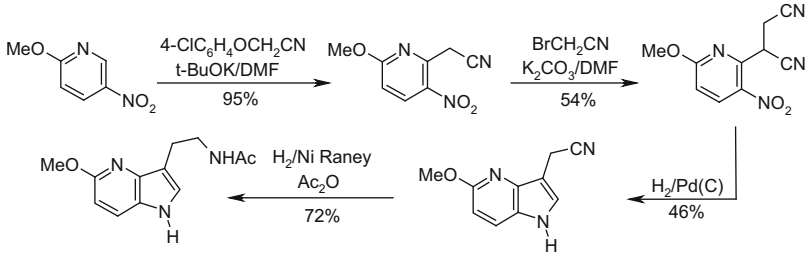
Scheme 67

The VNS cyanomethylation of 2-chloro-5-nitropyridine affords the corresponding nitropyridyl-substituted acetonitrile that undergoes hydrogenative cyclization into 5-chloro-6-azaindole (Scheme 68), a key starting material for the synthesis of potential Xa factor inhibitor [186].



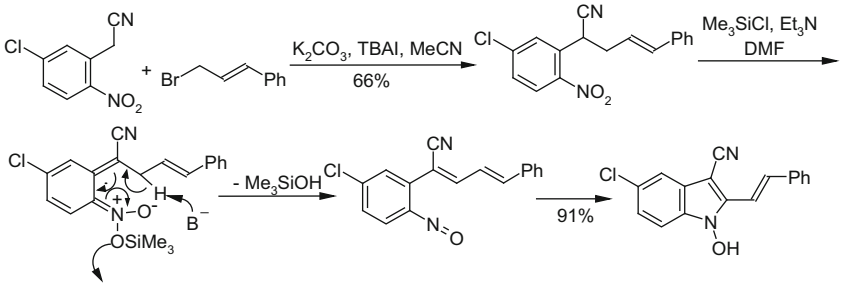
Scheme 68

A similar VNS cyanomethylation of 3-nitropyridine and subsequent hydrogenation of the so-formed *ortho*-nitropyridyl-substituted acetonitriles provided 4- and 6-azaindoles. The VNS of hydrogen in 2-methoxy-5-nitropyridine with the carbanion of aryloxyacetonitrile leads to pyridylacetonitrile. Alkylation of the latter with bromoacetonitrile followed by a two-step reduction efficiently results in the formation of 5-azamelatonin (Scheme 69) [187]. Condensation of pyridyl-substituted acetonitriles with aromatic aldehydes followed by catalytic reduction gave 3-benzyl-4-azaindoles [187].



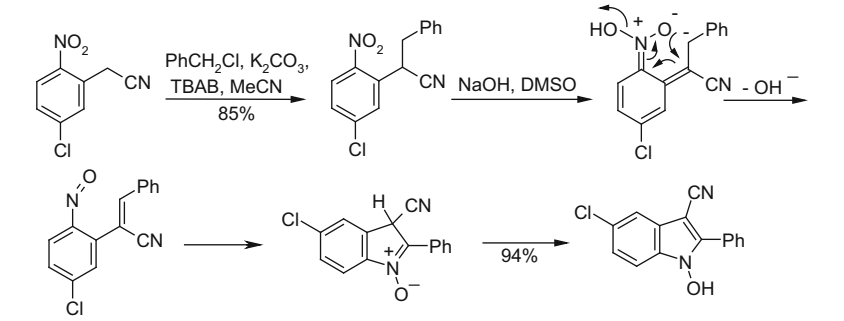
Scheme 69

There is one more way for conversion of *ortho*-nitroarylacetonitriles into indoles. Alkylation of such nitriles with allyl or benzyl halides followed by treatment of the compounds obtained with basic agents results in a multistep transformation, which is likely to proceed via intermediate nitrosoarenes, to produce 1-hydroxyindoles. For instance, alkylation of *ortho*-nitroarylacetonitriles with 3-phenylallyl bromide gives the compounds that in the presence of chlorotrimethylsilane and triethylamine undergo cyclization into 3-cyano-1-hydroxy-2-vinylindoles (Scheme 70) [188]. Presumably, this reaction proceeds via *O*-silylation of the nitronate anion and 1,5-elimination of trimethylsilanol from the intermediate trimethylsilyl nitronate, followed by cyclization and a hydrogen shift.



Scheme 70

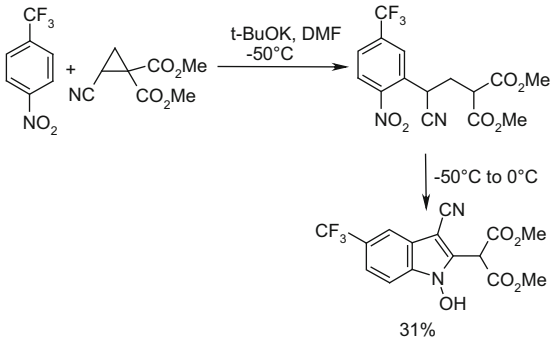
Another example of the reaction proceeding in a similar manner is the conversion of 2-(5-chloro-2-nitrophenyl)-3-phenylpropionitrile into *N*-hydroxyindole derivative (Scheme 71) [189]. The intermediate vinyl nitroso compound undergoes electrocyclization, resulting in the formation of nitrone (2*H*-indole N-oxide), which is tautomerized into *N*-hydroxyindole.



Scheme 71

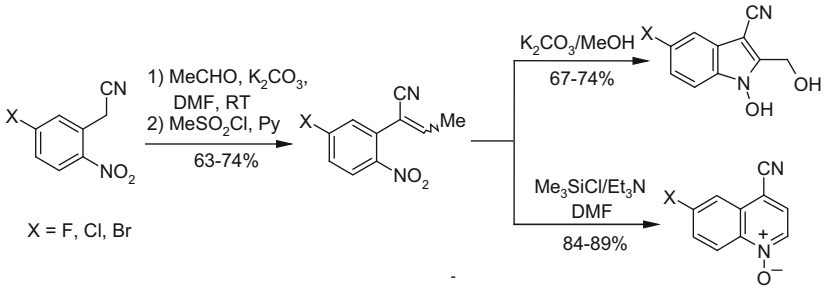
A peculiar way of formation of 1-hydroxyindole has been observed in the reaction of nitrobenzenes with dimethyl 2-cyanocyclopropane-1,1-dicarboxylate (Scheme 72) [190]. Treatment of 1-trifluoromethyl-4-nitrobenzene with this ester

at low temperature results in the VNS of hydrogen, proceeding via opening of the cyclopropane ring. Quenching of the reaction mixture at low temperature leads to 4-cyano-4-arylbutyric acid derivative; however, when the reaction mixture was allowed to warm-up to 0°C, cyclization into 1-hydroxyindole takes place via an intramolecular addition of the carbanion to the nitro group.



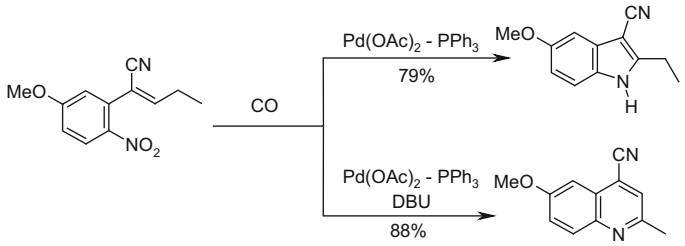
Scheme 72

The Knoevenagel condensation of alkyl *ortho*-nitroarylacetates and *ortho*-nitroarylacetonitriles with aliphatic aldehydes proved to give the corresponding alkylidene nitriles and esters [191–194]. In the presence of a base these nitriles undergo cyclization into indole or quinoline derivatives, depending on the reaction conditions (Scheme 73) [195].



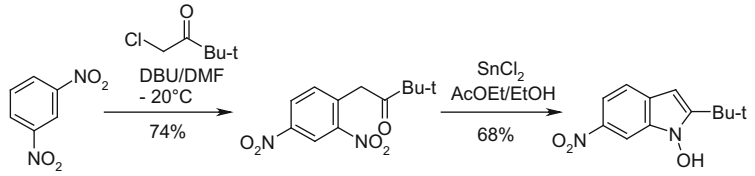
Scheme 73

Depending on the conditions, reduction of α-(2-nitroaryl)acrylonitriles with carbon monoxide can give two products (Scheme 74) [194]. Thus, reduction with palladium acetate–triphenylphosphine complex (neutral conditions) leads to indole-3-carbonitriles, while in the presence of DBU or t-BuOK (basic conditions) 4-cyanoquinoline was formed.



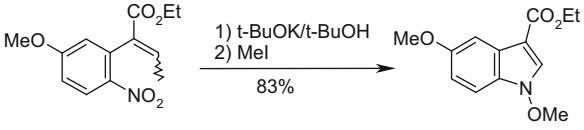
Scheme 74

The VNS in *meta*-dinitrobenzene by action of carbanions of α-haloketones leads to 2,4-dinitrobenzyl ketones, which can be reduced to 1-hydroxy-6-nitroindoles under mild conditions with tin(II) chloride (Scheme 75) [196].



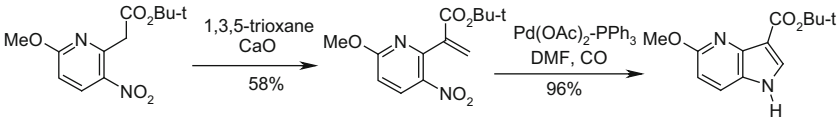
Scheme 75

The VNS reaction of 4-nitroanisole with ethyl chloroacetate followed by the Knoevenagel condensation of the product with acetaldehyde affords α-(2-nitrophenyl)crotonate, which in the presence of *t*-BuOK in *tert*-butanol undergoes cyclization into *N*-hydroxyindole-3-carboxylate (Scheme 76). Further alkylation of the latter compound with methyl iodide results in *N*-methoxyindole. It is worth mentioning that in this reaction a partial loss of the alkene chain does happen to occur [194]. A similar phenomenon has been observed earlier in our laboratory [195].



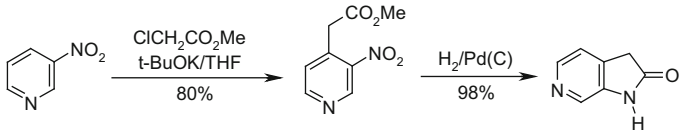
Scheme 76

The reaction of 2-nitroarylacetonitriles and their heteroanalogues with trioxane has been reported to afford α-(2-nitroaryl)acrylates and their heteroanalogues, which can be reduced with carbon monoxide in the presence of palladium acetate–triphenylphosphine complex to give esters of the corresponding indole-3-carboxylic acids in high yields (Scheme 77) [193].



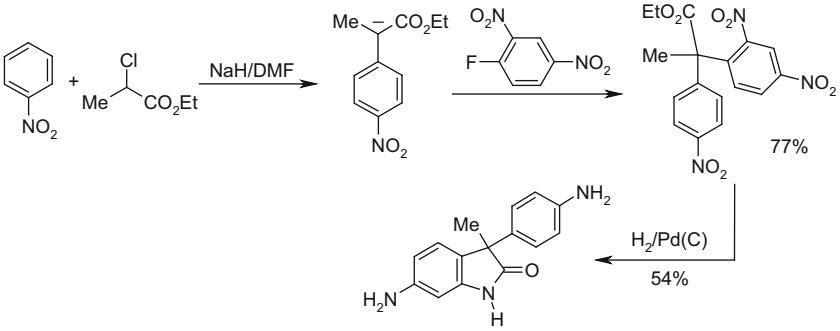
Scheme 77

The reaction of 3-nitropyridine with methyl chloroacetate under basic conditions provides ethyl nitropyridyl acetates, followed by their catalytic hydrogenation and cyclization into azaoxindoles (Scheme 78) [59, 60, 197].



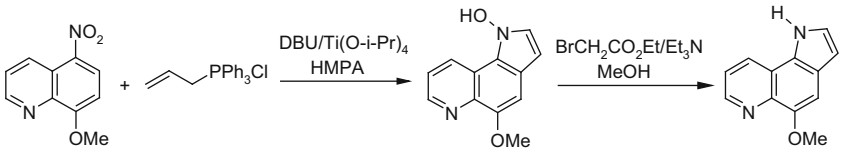
Scheme 78

The VNS reaction of nitrobenzene with ethyl α-chloropropionate, proceeding in the *para*-position of the benzene ring, can be followed in situ by the S_NAr of fluorine atom in subsequently added 1-fluoro-2,4-dinitrobenzene to give 2,4,4′-trinitrodiarylpropionate, which being hydrogenated is transformed into 3-aryloxindole derivative (Scheme 79) [198, 199].



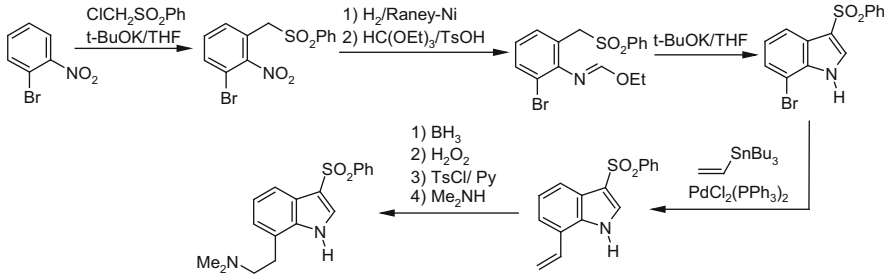
Scheme 79

Phosphonium ylide, generated from allyl triphenylphosphonium chloride, is capable of addition to 1-nitronaphthalene or 5-nitro-8-methoxyquinoline in the presence of DBU and titanium tetraisopropoxide to form unstable *N*-hydroxyindole derivative, which is transformed by action of ethyl bromoacetate into benzo- or pyridoindoles (Scheme 80) [200].



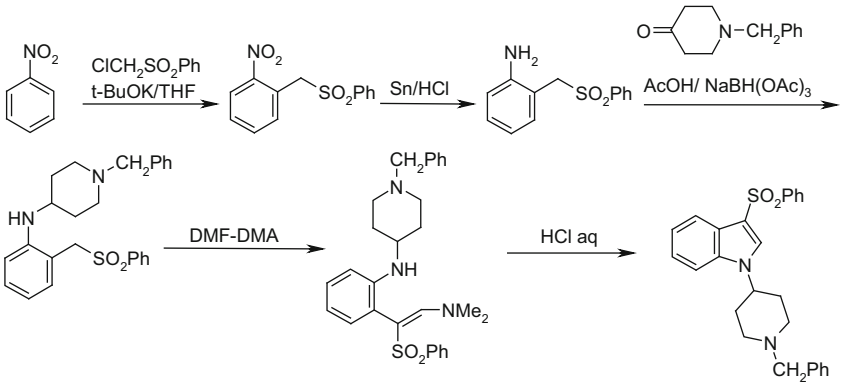
Scheme 80

ortho-Nitrobenzyl aryl sulfones, readily available via the VNS reactions of nitroarenes with the carbanions of chloromethyl aryl sulfones, upon reduction and conversion of the amino group into imidate [201–203] or imine [204] functionality, are able to undergo cyclization into substituted indoles. This procedure is particularly useful due to the possibility to direct the VNS reaction selectively in *ortho*-position to the nitro group when the reaction is carried out in t-BuOK/THF (Scheme 81) [25]. This approach was used for the synthesis of 5- and 7-bromo-3-sulfonylindoles that were subsequently functionalized by the Stille coupling with tributyl(vinyl)tin. The obtained vinyl derivatives were then transformed into the corresponding amino compounds, tested as norepinephrine reuptake inhibitors and 5-HT_{2A} receptor antagonists [202].



Scheme 81

Alternatively, N-substituted 3-phenylsulfonylindoles have been synthesized via reductive *N*-alkylation of *ortho*-aminobenzyl sulfones with ketones followed by condensation with dimethylformaldehyde dimethylacetal and cyclization (Scheme 82) [203].



Scheme 82

In this section we have presented numerous ways to construct indole derivatives via nucleophilic substitution of hydrogen. It has been shown that this approach is one of the simplest, versatile, and efficient ways to such ring systems, which can easily be adopted for large-scale operations. Another advantage of this methodology is that in contrast to the majority of modern methods no transition metals are used, so troublesome removal of their impurities from the final products is not necessary [205].

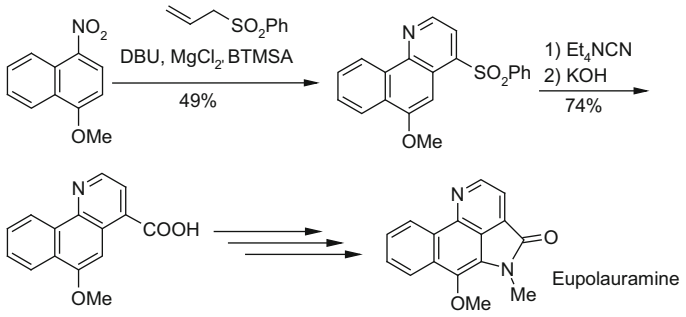
6.2 *Quinolines*

Since the quinoline ring system is often encountered in pharmaceuticals, plant protection agents, photoactive compounds, etc., a search for new synthetic pathways to quinoline derivatives continues to be of a substantial interest. There are numerous examples of synthesis of quinolines and their condensed analogues via nucleophilic substitution of hydrogen in nitroarenes. One can classify those into two broad categories:

a. Direct syntheses, when the quinoline ring system is formed directly, or as result of the domino reaction from the intermediate σ^H adducts
b. Products of nucleophilic substitution of hydrogen are subsequently converted into quinolines

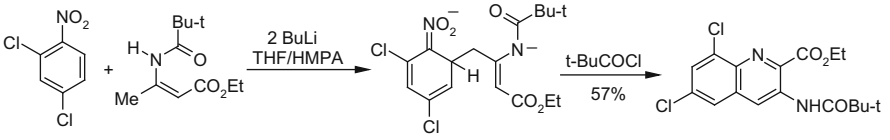
Direct methods are based on the reactions of nitroarenes or nitroheteroarenes with carbanions affording the intermediate σ^H adducts that, under the reaction conditions, are converted into nitrosoarenes according to the intramolecular redox stoichiometry. The nitrosoarenes are known to be rather active electrophilic partners and are able to enter in situ further reactions to produce quinolines as the ultimate products.

An important example is the formal synthesis of eupolauramine, an alkaloid from the bark of the African plant *Eupomatia laurina*. This approach involves addition of the carbanion of allyl phenyl sulfone to 1-methoxy-4-nitronaphthalene followed by conversion of the σ^H adduct formed into the corresponding nitrosoarene. Further intramolecular condensation affords phenylsulfonyl-substituted azaphenanthrene (Scheme 83) [82]. The sulfone obtained was transformed into tricyclic azaaromatic acid, from which in turn the final alkaloid can be obtained following the known procedure [206].



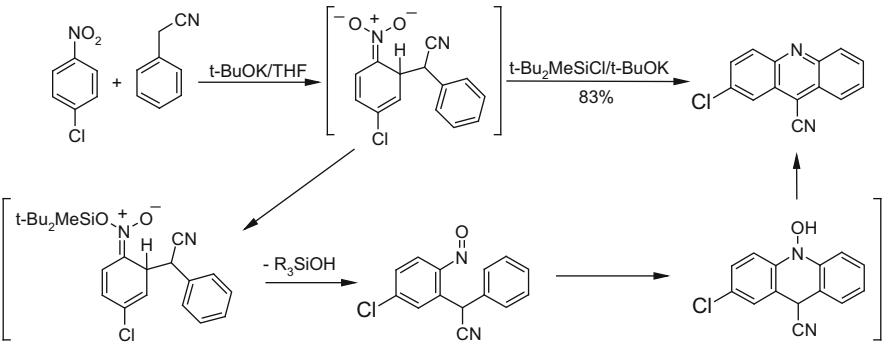
Scheme 83

A novel pathway for the synthesis of substituted 3-aminoquinolines, proceeding via addition of the dianion of 3-aminocrotonates to nitroarenes, is exemplified by the reaction of ethyl *N*-pivaloyl-3-aminocrotonate with 2,4-dichloronitrobenzene. The intermediate σ^H adduct upon silylation or acylation is transformed into the corresponding ethyl 3-(*N*-pivaloyl amino)quinoline-2-carboxylate (Scheme 84) [207].



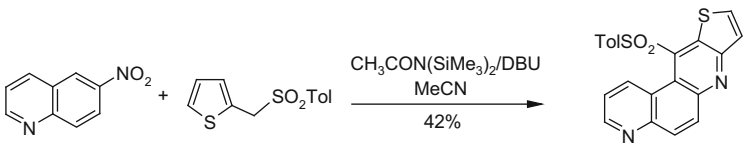
Scheme 84

There are numerous examples of construction of condensed pyridines (and also quinolines and acridines) via cascade reactions, involving conversion of the σ^H adducts of benzylic or allylic carbanions to nitroarenes followed by their intramolecular cyclization to form the pyridine ring. Thus, the reaction between 4-chloronitrobenzene and phenylacetonitrile, which is known to produce in protic media the corresponding 2,1-benzisoxazole via conversion of the intermediate σ^H adduct into nitrosoarene and its further condensation reaction [80], can proceed in aprotic media along another way. The same σ^H adduct formed in tetrahydrofuran, when treated with trialkylchlorosilanes or pivaloyl chloride, undergoes cyclization into acridine derivative (Scheme 85) [208].



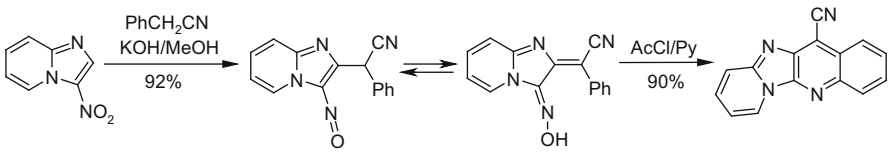
Scheme 85

A similar reaction has been observed to proceed between 6-nitroquinoline and thienylmethyl tolyl sulfone in aprotic acetonitrile. The intermediate σ^H adduct, being treated with *bis*-trimethylsilyl acetamide, is converted into nitrosoarene, which undergoes intramolecular condensation to give thienophenanthroline in good yield (Scheme 86) [209].



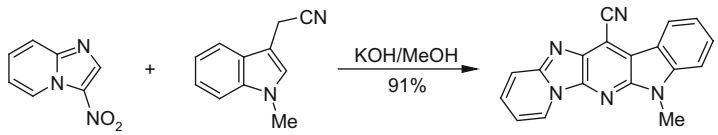
Scheme 86

Analogous transformation was reported to proceed between arylacetonitriles and 3-nitroimidazo[1,2-a]pyridine, thus leading to pyrido-annelated imidazoquinolines (Scheme 87) that are of interest as highly fluorescent dyes [130].



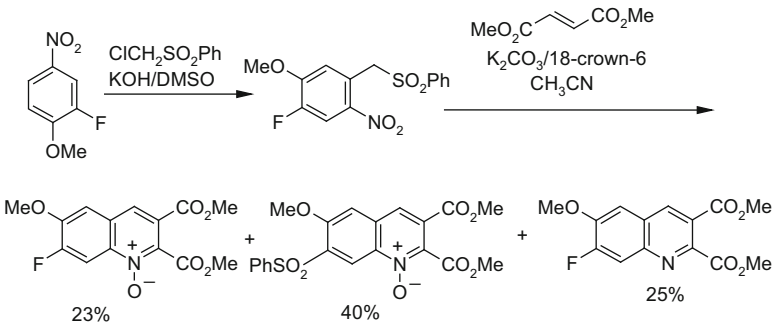
Scheme 87

The reaction of the same nitroimidazopyridine with 3-indolylacetonitrile leads directly to pentacyclic azaaromatic system (Scheme 88) [210].



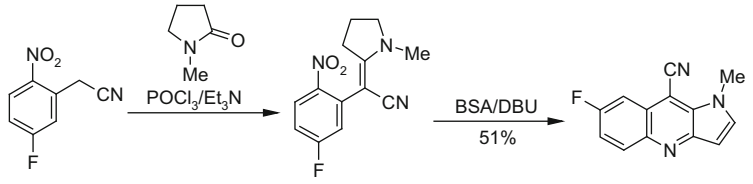
Scheme 88

Syntheses of quinolines from the products of the nucleophilic substitution of hydrogen proved to be also valuable. For instance, *ortho*-nitrobenzyl sulfones react with dialkyl maleates and fumarates to produce directly quinoline 2,3-dicarboxylate N-oxides [211]. The reaction proceeds via the Michael addition of the nitrobenzyl carbanion followed by elimination of benzenesulfinic acid and subsequent intramolecular addition of the allylic carbanion to the nitro group. This approach has recently been used for the synthesis of fluorine-substituted quinoline N-oxides (Scheme 89) [212].



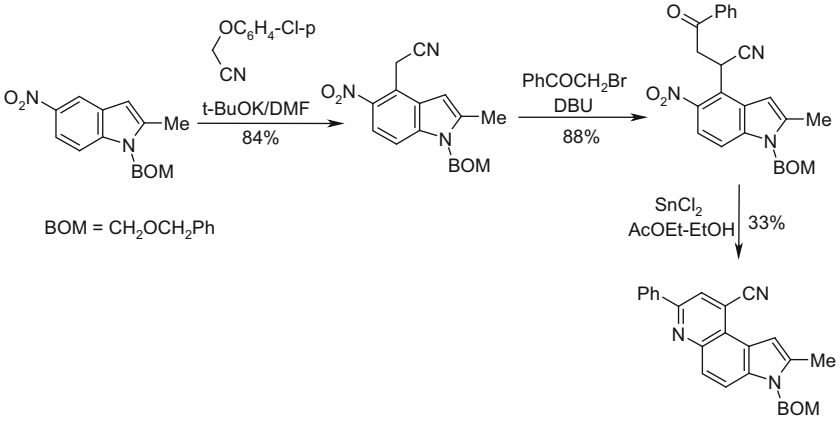
Scheme 89

The reaction of *ortho*-nitroarylacetonitriles with the Vilsmeier–Haack reagent, prepared from *N*-methylpyrrolidone, followed by intramolecular cyclization, induced by diazabicycloundecene (DBU) in the presence of *bis*-trimethylsilylacetamide (BSA), leads directly to pyrrolo[3,2-*b*]quinoline derivatives (Scheme 90) [213].



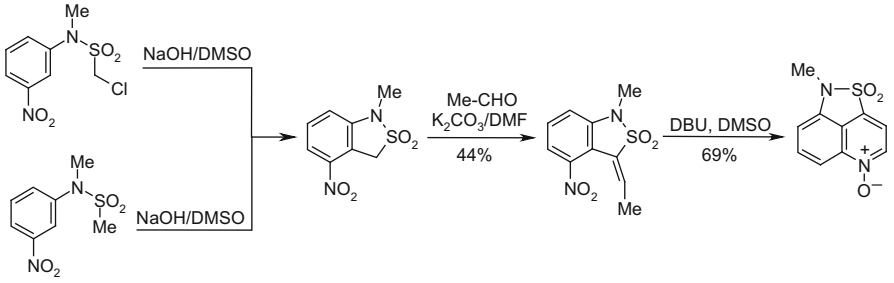
Scheme 90

A versatile synthesis of pyrrolo-annelated quinolines has been reported to occur via alkylation of the VNS products, *ortho*-nitroaryl-substituted acetonitriles, with α-bromoketones. The obtained ketonitriles can be reduced under mild conditions with tin(II) chloride in ethyl acetate–ethanol mixture into quinoline-4-carbonitriles [214]. The same reaction sequence has been applied to 5-nitroindol-4-yl- and 4-nitroindol-5-yl-acetonitriles to obtain tricyclic 4-cyano-2-phenyl derivatives of pyrrolo[3,2-*f*]- and pyrrolo[2,3-*h*]-quinolines (Scheme 91) [214].



Scheme 91

Nitrobenzosultams obtained by intramolecular vicarious [215] or oxidative nucleophilic substitution of hydrogen [216] in *N*-chloromethylsulfonyl- or *N*-methylsulfonyl-substituted *meta*-nitroanilides have been reported to enter the Knoevenagel condensation with acetaldehyde [217]. The formed ethylidene sultam, when treated with DBU, undergoes cyclization into the tricyclic sultam system, bearing the quinoline N-oxide fragment (Scheme 92) [217]. The reaction appears to proceed via intramolecular addition of the allylic carbanion to the nitro group.



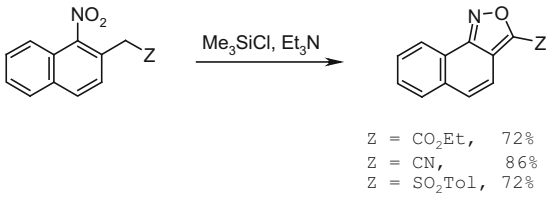
Scheme 92

6.3 2,1-Benzisoxazoles

The 2,1-benzisoxazole (anthranil) ring system is of interest as a key intermediate for the synthesis of other heterocycles. 2,1-Benzisoxazoles can be derived from the direct multistep domino reaction of some carbanions with nitroarenes or by conversion of the products of nucleophilic substitution of hydrogen in nitroarenes. As early as in 1960, Davis and Pizzini reported that the reaction of 4-chloronitrobenzene with phenylacetonitrile in the presence of potassium hydroxide in protic media affords 3-phenyl-5-chloro-2,1-benzisoxazole in high yield [80] (Scheme 17).

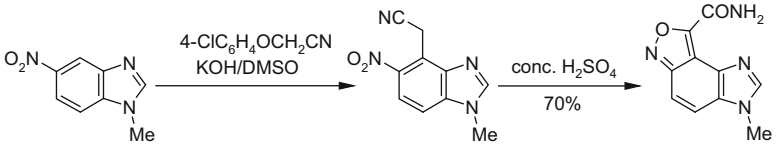
This is in fact a general way for the synthesis of 2,1-benzisoxazoles, which have found wide application as starting materials to obtain other heterocyclic systems: quinolines [218–221], polyquinolines [222–224], acridines [80, 225–227], and benzodiazepines [228]. The most common approach is reduction of anthranils to 2-aminobenzophenones, which are appropriate starting materials to build other heterocyclic systems.

ortho-Nitroarylacetic esters, nitriles, and *ortho*-nitrobenzylsulfones, available via the VNS methodology, are readily converted into 2,1-benzisoxazoles through condensation on treatment with chlorotrimethylsilane in the presence of triethylamine (Scheme 93) [229].



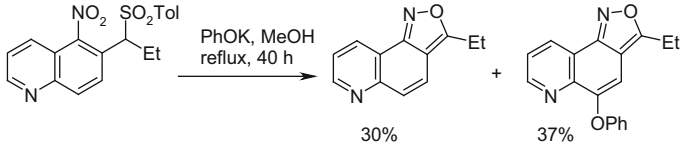
Scheme 93

Alternatively, *ortho*-nitroaryl-substituted acetonitriles and their heteroanalogues can be dehydrated into benzisoxazoles on treatment with concentrated sulfuric acid (Scheme 94) [230].



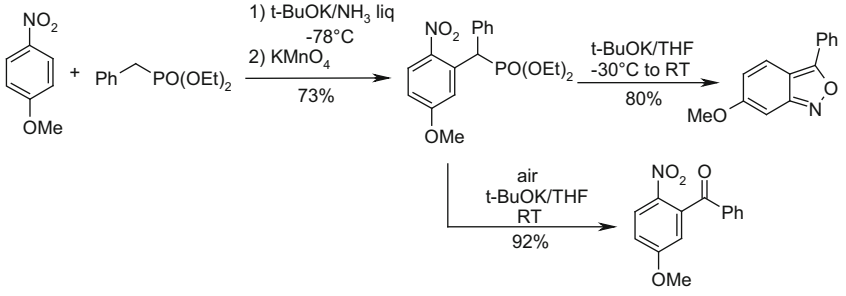
Scheme 94

The formation of 2,1-benzisoxazoles has also been observed when the VNS products derived from bicyclic nitroarenes and heteroarenes have been allowed to react with phenolate and thiolate anions (Scheme 95), as well as with some carbanions [231].



Scheme 95

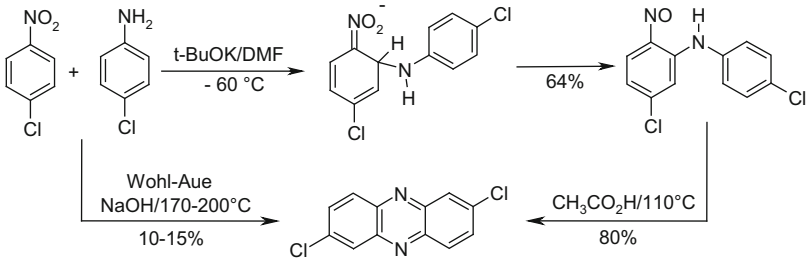
Benzisoxazoles can readily be obtained by anaerobic, spontaneous transformation of carbanions of α-(*ortho*-nitroaryl)benzyl phosphonates, derived from the ONSH in nitroarenes with carbanion of diethyl benzylphosphonate, whereas oxygen oxidation of such carbanions gives nitrobenzophenones (Scheme 96) [232].



Scheme 96

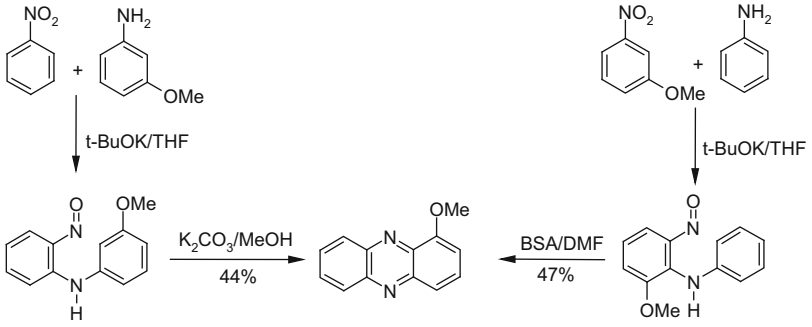
6.4 *Phenazines and Other Heterocyclic Compounds from 2-Nitrosodiphenylamines*

It has recently been found in our laboratory that anilines react with nitroarenes in the presence of a strong base to form 2-nitrosodiphenylamines [86]. The reaction proceeds via addition of the N-anion of anilines to nitroarenes in the *ortho*-position to the nitro group, followed by conversion of the formed σ^H adduct according to an intramolecular redox stoichiometry (Scheme 97). The reaction is of general character; thus, a variety of 2-nitrosodiphenylamines become readily available. These compounds are versatile starting materials for the synthesis of heterocycles containing two nitrogen atoms: phenazines, benzimidazoles, quinoxalines, etc. Simple treatment of 2-nitrosodiphenylamines with acetic acid leads to phenazines in high yields.



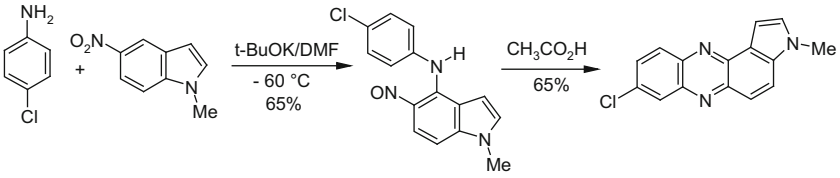
Scheme 97

This two-step process is analogous to, but much more efficient than, the classic Wohl–Aue synthesis of phenazines [233]. The versatility of this approach has been demonstrated by the synthesis of 1-methoxyphenazine that can be obtained from two different pairs "nitroarene–aniline", namely, nitrobenzene–*meta*-anisidine or *meta*-nitroanisole–aniline (Scheme 98) [84].



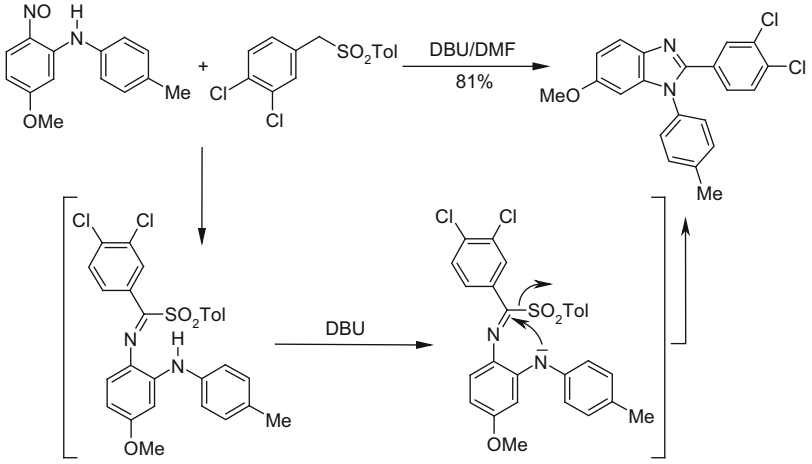
Scheme 98

Availability of nitroarenes and anilines opens almost unlimited simple and efficient access to phenazines, as well as to their derivatives condensed with an additional ring, as exemplified by the synthesis of pyrrolo[3,2-*b*]phenazine from 5-nitroindoles (Scheme 99) [234].



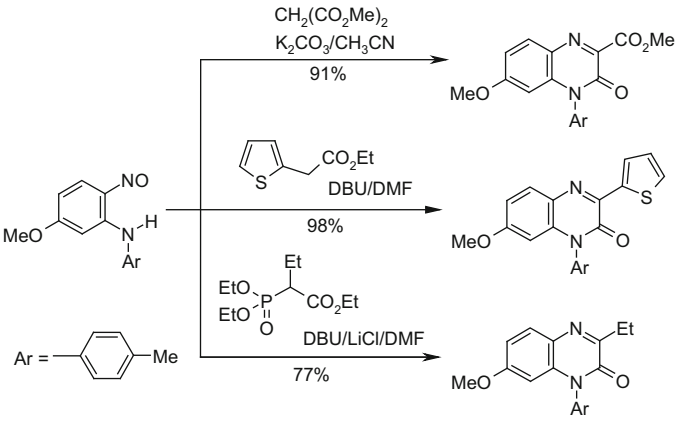
Scheme 99

Carbanions of benzyl aryl sulfones are able to react with 2-nitrosodiphenylamines to produce 1,2-diarylbenzimidazoles. The reaction appears to proceed via attack of these carbanions on the nitroso group followed by intramolecular addition–elimination process to give benzimidazoles (Scheme 100) [83].



Scheme 100

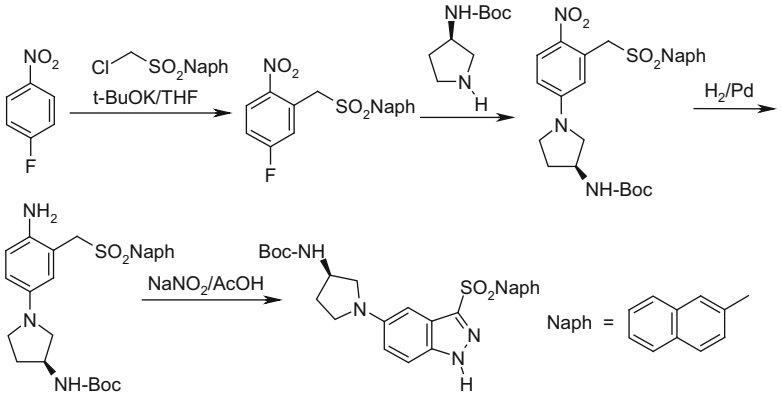
Condensation of 2-nitrosodiphenylamines with a variety of highly stabilized carbanions of dialkyl malonates, alkyl phenylacetates, and trialkyl phosphonoacetates is an efficient way for the synthesis of a great deal of substituted *N*-arylquinoxalin-2(1*H*)-ones (Scheme 101) [235, 236]. Double additions of anions of 2-cyanoalkyl carboxylates to 2-nitroso-4-alkylaminodiphenylamines result in the formation of pyrroloquinoxalinones [236].



Scheme 101

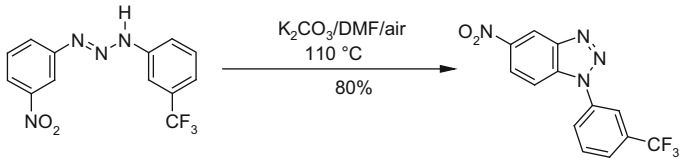
6.5 *Miscellaneous Syntheses of Heterocycles*

3-Arylsulfonylindazoles, novel 5-HT_6 receptor antagonists, have been synthesized via the VNS reactions of *para*-substituted nitrobenzenes with carbanion of chloromethyl aryl sulfones followed by hydrogenation of the nitro group (Scheme 102). Further reaction of *ortho*-aminobenzyl sulfones with sodium nitrite-acetic acid gave the desired 5-substituted indazoles of potential biological activity [237, 238].



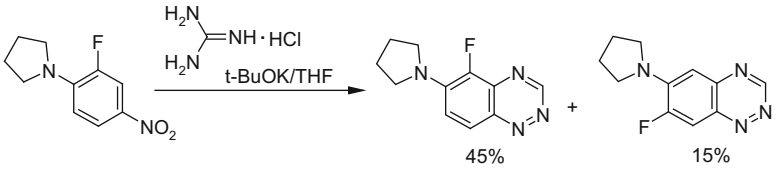
Scheme 102

Oxidative intramolecular amination of *meta*-nitro-substituted diaryl triazenes has been established to proceed under mild basic conditions in the presence of K_2CO_3 in DMF (Scheme 103) [239].



Scheme 103

Conversion of the initially formed σ^H adducts into intermediate nitrosoarenes appears to be involved in the reaction of nitroarenes with guanidines, leading to 3-amino-1,2,4-benzotriazines (Scheme 104) [240]. The mechanism of this transformation proposed by the authors includes oxidation of the intermediate σ^H adduct to form the corresponding 2-nitrophenyl-substituted guanidine, which undergoes cyclization into 3-amino-1,2,4-benzotriazine-1-oxide. An alternative mechanism can be suggested that involves reduction of the nitro group to the nitroso one, followed by cyclization resulting in the N=N bond formation. Partial reduction of the nitro group was observed earlier in the reactions of cyclic (3-nitrophenyl) guanidines [241].



Scheme 104

7 Conclusion

From the data presented it is evident that nucleophilic substitution of hydrogen is an efficient synthetic tool for introduction of a variety of substituents into heterocyclic rings and construction of heterocyclic systems. We do hope that numerous examples of nucleophilic substitution of hydrogen, as well as use of this versatile and general reaction for the synthesis of heterocyclic compounds will attract attention of researchers working in the field of organic synthesis.

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

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

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

Contents

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1 Introduction

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

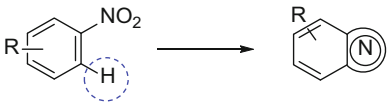
In this review, we consider aromatic nitro compounds (nitroarenes) with the vacant *ortho*-position relative to the nitro group, as a basis for the synthesis of condensed nitrogen heterocycles (benzo-annelated N-heterocycles) (Scheme 1).

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

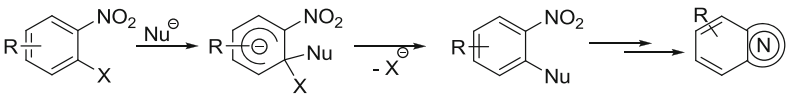
On the other hand, if hydrogen atoms occupy the *ortho*-positions relative to the nitro group, a nucleophile addition might also result in the formation of anionic σ^H-complexes. However, their further transformations are hampered because the hydride ion (a formal leaving group) is a thermodynamically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

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

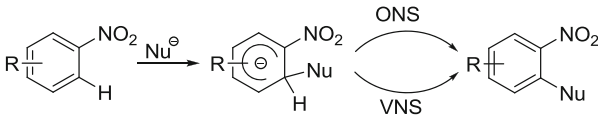
In the following sections of this chapter, we will consider some other possibilities for the formation of heterocyclic compounds by using functionalization of C–H fragments in nitroarenes.



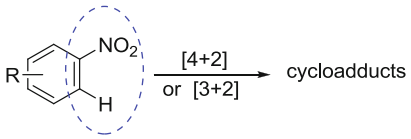
Scheme 1 Nitroarenes with unsubstituted *ortho*-position as a basis for the synthesis of N-heterocycles



Scheme 2 Nucleophilic *ipso*-substitution in nitroarenes



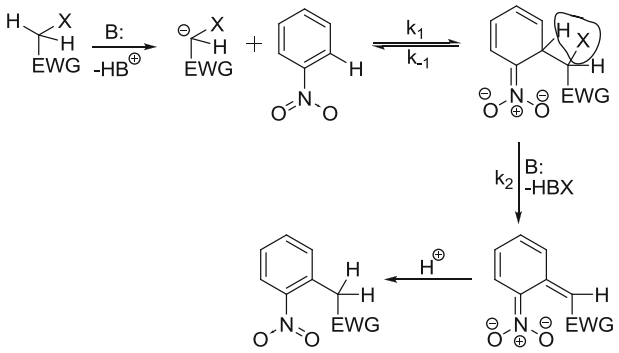
Scheme 3 S_N^H reactions of nitroarenes



Scheme 4 Cycloadditions to nitroarenes

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

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



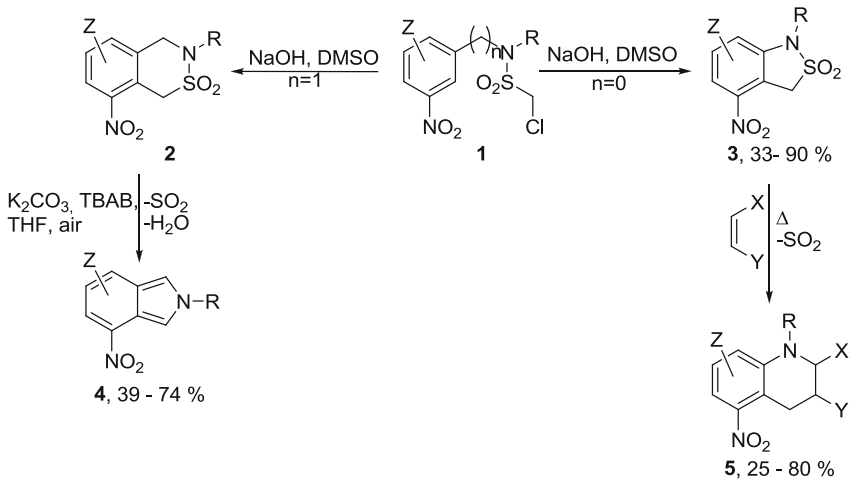
Scheme 5 Vicarious nucleophilic substitution of hydrogen (general scheme)

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

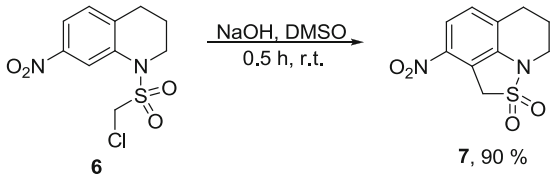
In this section, we will focus on two main approaches to the synthesis of condensed N-heterocycles based on nitroarenes using the S_N^H methodology: vicarious nucleophilic substitution of hydrogen (VNS) and oxidative nucleophilic substitution of hydrogen (ONS).

2.1 *Vicarious Nucleophilic Substitution of Hydrogen*

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



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



Scheme 7 Synthesis of tricyclic sulfonamides

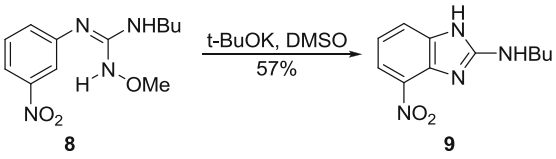
σ^H-adducts is much faster than the reverse reaction ($k_2[B] >> k_{-1}$) [18, 19], the ratio of products reflects the ratio of rate constants k_1 for the addition step.

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

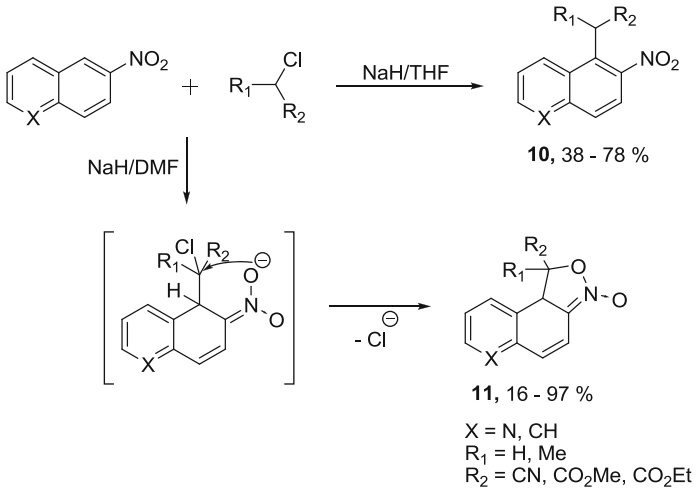
The formation of heterocycles by the VNS methodology has been shown to occur either by direct intramolecular VNS processes or through transformations of the *ortho*-nitrobenzyl derivatives resulting from intermolecular VNS reactions.

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

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



Scheme 8 Synthesis of benzimidazole through the VNS reaction



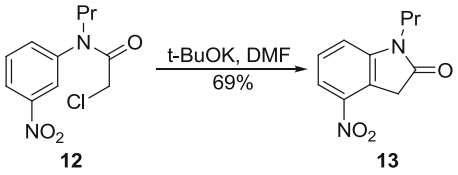
Scheme 9 Synthesis of benzo-fused cyclic nitronates

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

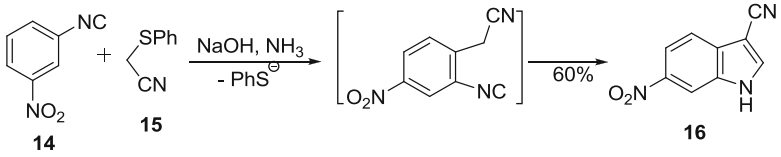
2-Nitronaphthalene and 6-nitroquinoline have been found to react easily with 2-chloronitriles and the corresponding esters in the presence of NaH [27] (Scheme 9). Depending on solvent, it is possible to obtain either VNS products **10** or cyclic nitronates **11**.

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

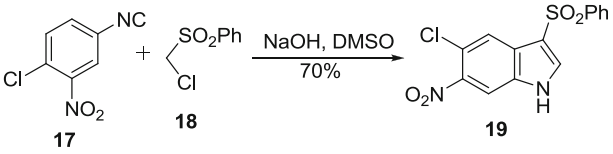
A number of publications deal with the use of nitroaryl isocyanides as direct precursors of nitroindoles. The starting isocyanides have been obtained by using the VNS reactions. Thus, in the reaction of 3-isocyanonitrobenzene **14** with



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



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



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

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

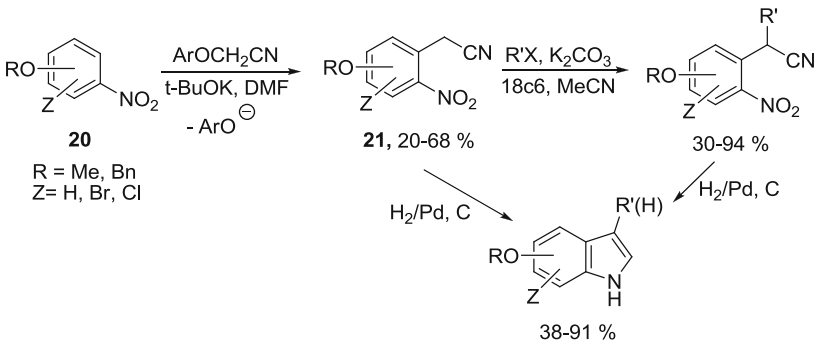
A similar reaction of compound **17** with phenyl(chloromethyl)sulfone **18**, as a vicarious nucleophile, affords 3-sulfonylindole **19** [29] (Scheme 12).

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

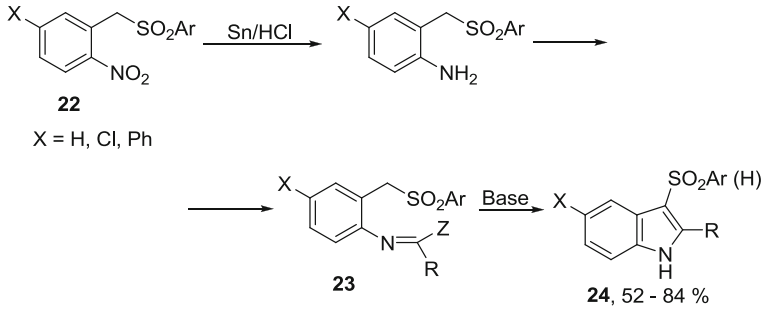
This approach is nicely illustrated by cyanomethylation of substituted nitrobenzenes **20** [30, 31], followed by hydrogenation of *ortho*-nitroacetonitriles **21** [32, 33] (Scheme 13).

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

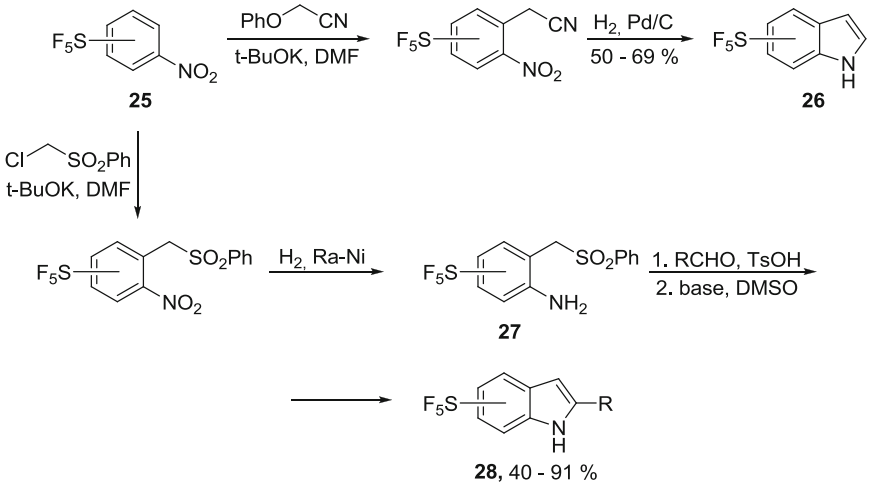
Both approaches described above have been used for the synthesis of indoles bearing the pentafluorosulfanyl group [36, 37]. The reaction of *meta*- and *para*-nitro (pentafluorosulfanyl)benzene **25** with phenoxyacetonitrile (Scheme 15) under VNS conditions followed by hydrogenation gave rise to SF_5-substituted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



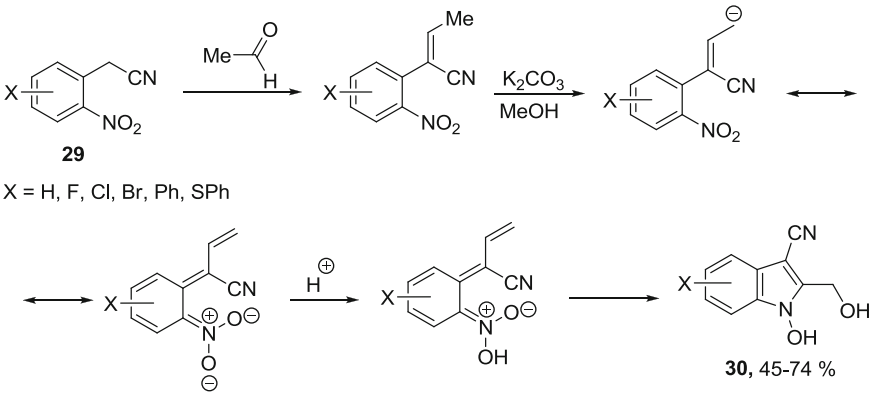
Scheme 13 Heterocyclizations of *ortho*-nitrophenyl acetonitriles



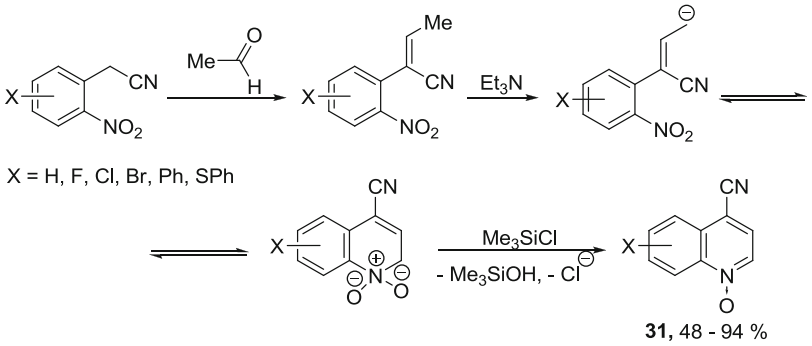
Scheme 14 Synthesis of 3-sulfonylindoles



Scheme 15 VNS approach to pentafluorosulfanyl-substituted indoles



Scheme 16 Synthesis of N-hydroxyindoles



Scheme 17 Synthesis of quinoline N-oxides

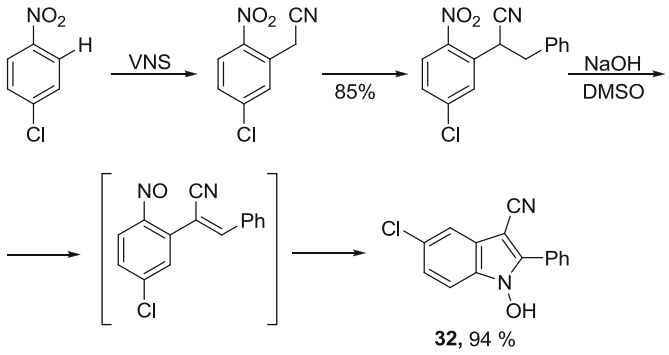
An aromatic nitro group sometimes participates in the formation of indoles, in particular of N-hydroxy derivatives. For example, the reaction of *ortho*-nitroaryl substituted acetonitriles **29** with acetaldehyde followed by treatment with K_2CO_3 afforded N-hydroxyindoles **30**, as the major products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

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

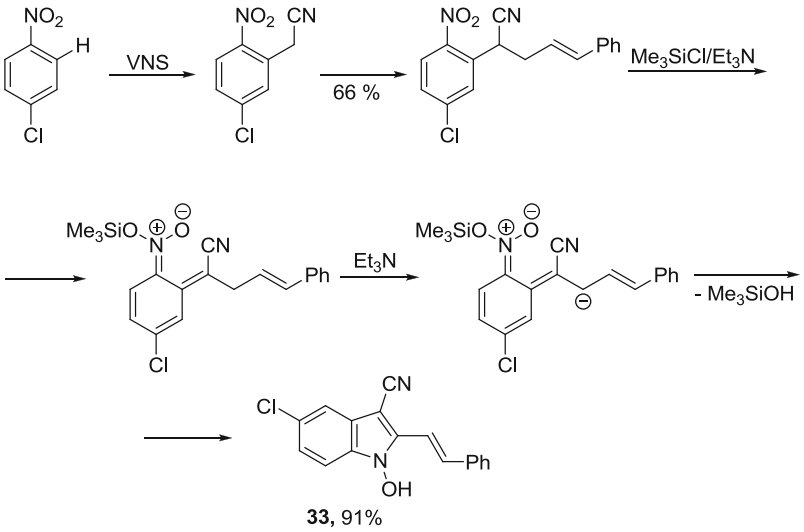
Polyfunctional N-hydroxyindole derivatives **32** have been synthesized by using the sequence of reactions, involving the VNS of hydrogen, alkylation, and base-catalyzed cyclization [39] (Scheme 18).

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

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



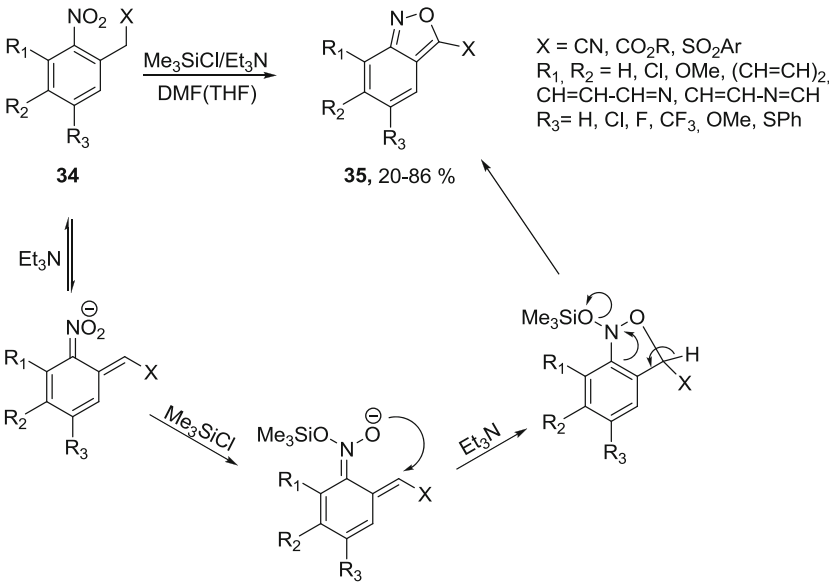
Scheme 18 Synthesis of N-hydroxy-substituted indoles



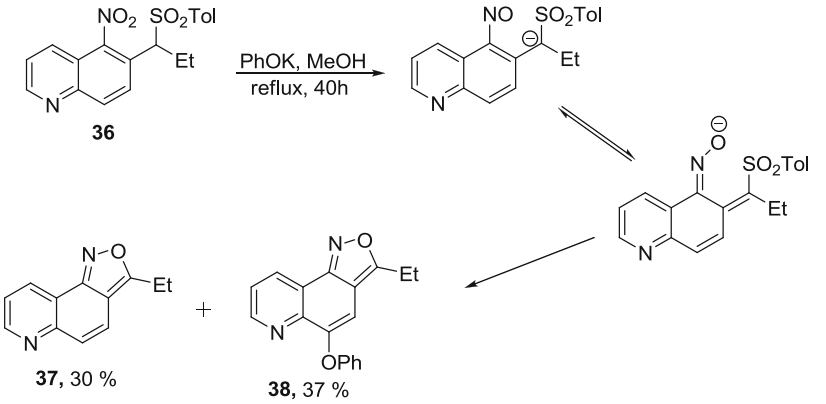
Scheme 19 Synthesis of N-hydroxy-substituted indoles

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

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



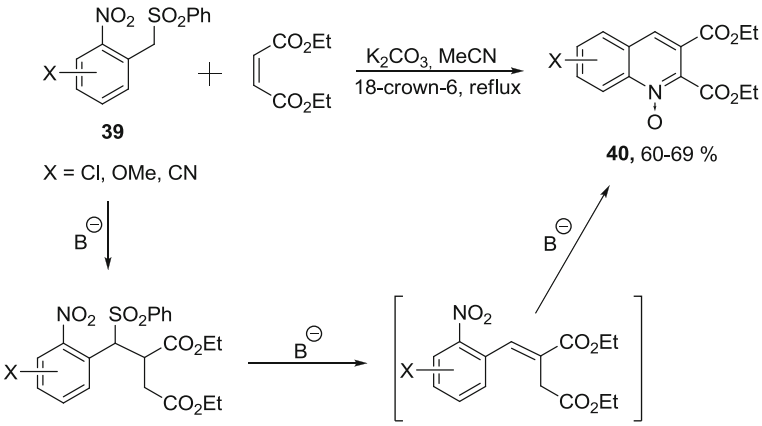
Scheme 20 Annelation of the isoxazole ring to *ortho*-nitrobenzyl derivatives



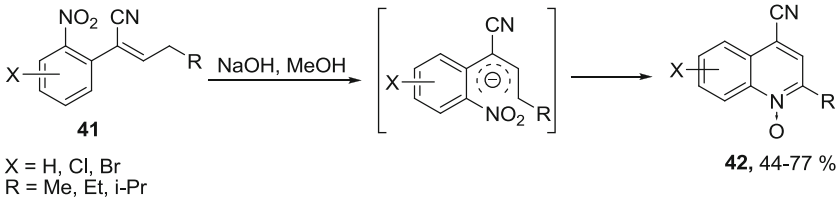
Scheme 21 Synthesis of isoxazoloquinolines

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

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



Scheme 22 Synthesis of quinoline N-oxides

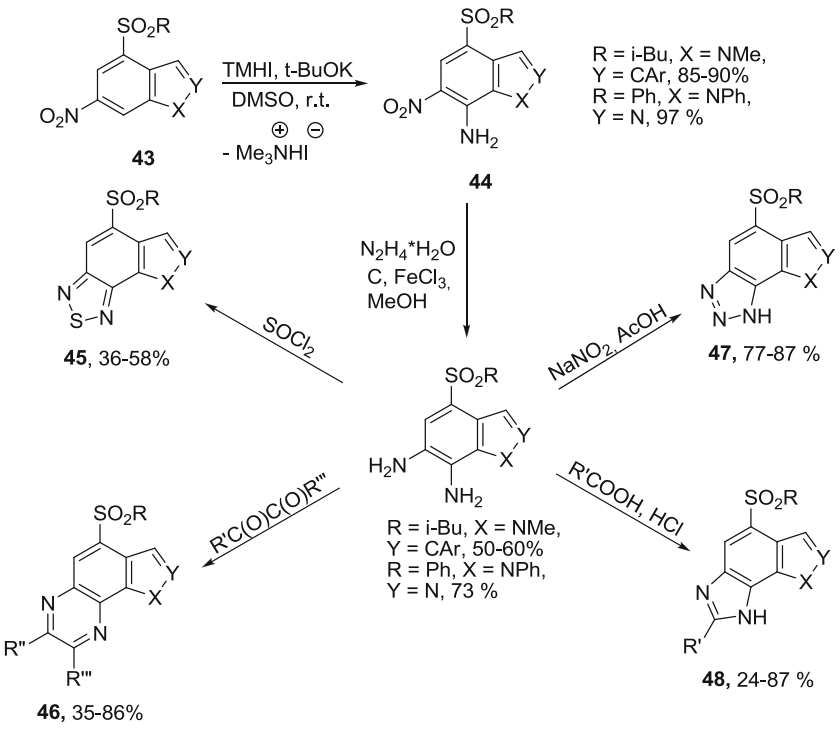


Scheme 23 Synthesis of quinoline N-oxides

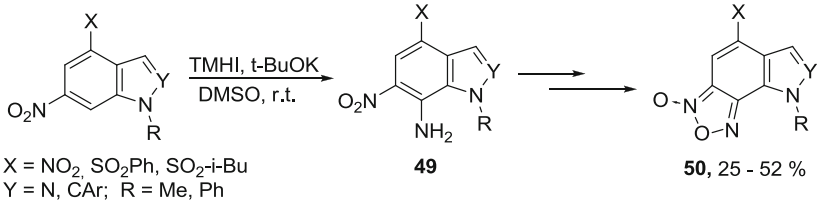
Nitroamines **44** as well as their analogues **49** were used for the synthesis of tricyclic furoxan derivatives **50** [46–48] (Scheme 25).

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

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



Scheme 24 Heterocyclizations of fused *ortho*-phenylenediamines

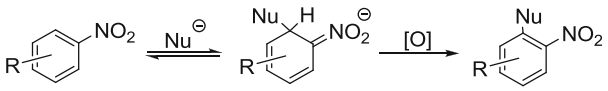


Scheme 25 Synthesis of condensed benzofuroxans

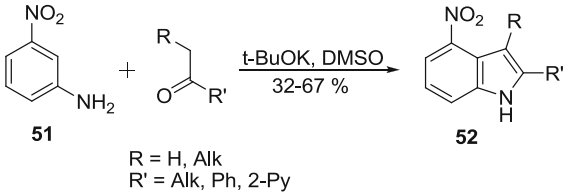
2.2 *Oxidative Nucleophilic Substitution of Hydrogen*

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

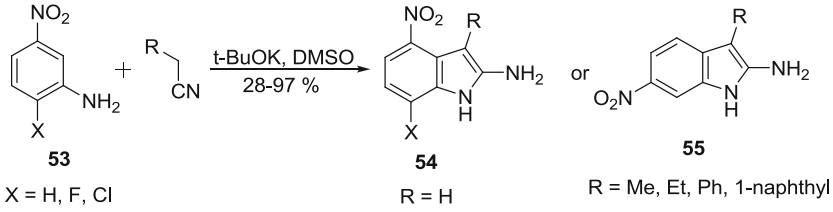
The ONS reactions usually occur at the *ortho*- and/or *para*-positions of nitroarenes relative to the nitro group depending on the structure of reagents.



Scheme 26 Oxidative nucleophilic substitution of hydrogen (general scheme)



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



Scheme 28 The ONS approach to 2-aminoindoles

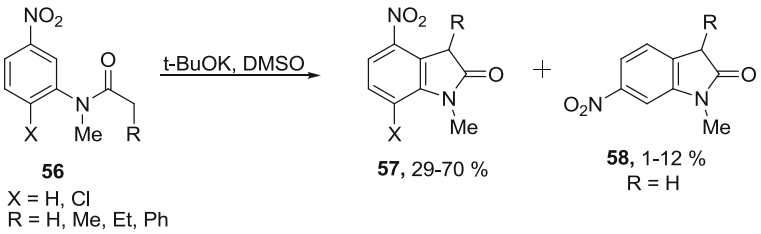
It is a common knowledge that ONS reactions allow one to introduce substituted alkyl fragments or heteroatom functional groups in nitroarenes. There are plenty of examples illustrating intramolecular ONS processes leading to the formation of heterocyclic compounds. However, in this section, we will focus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

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

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

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

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

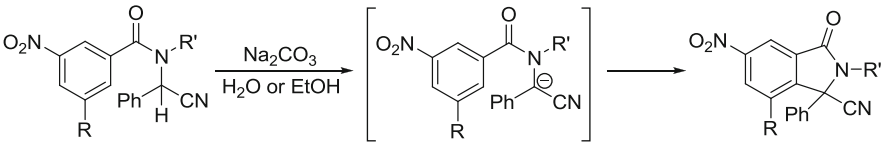


56
X = H, Cl
R = H, Me, Et, Ph

57, 29-70 %

58, 1-12 %
R = H

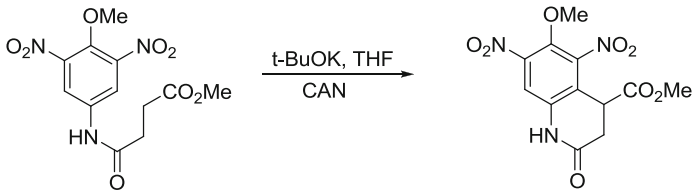
Scheme 29 Synthesis of substituted 2-oxoindoles



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

60, 20 - 62 %

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



61

62, 55%

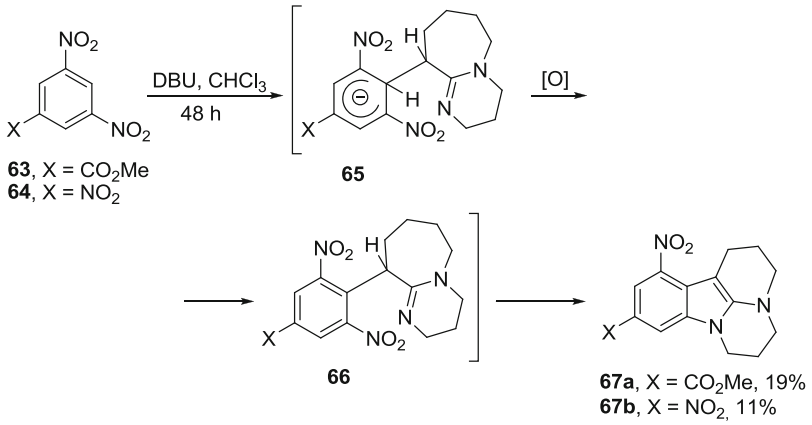
Scheme 31 Application of ONS to the synthesis of natural products

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

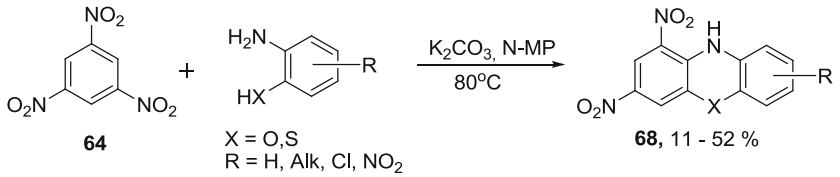
Another example, illustrating use of intramolecular ONS reactions for the synthesis of N-heterocycles, is shown in Scheme 31. In this case, the annelation of a six-membered heterocycle proceeds by action of *t*-BuOK as base and CAN as an oxidant. The cyclization product **62** seems to be intermediate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

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

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



Scheme 32 Reaction of polynitrobenzenes with DBU



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

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

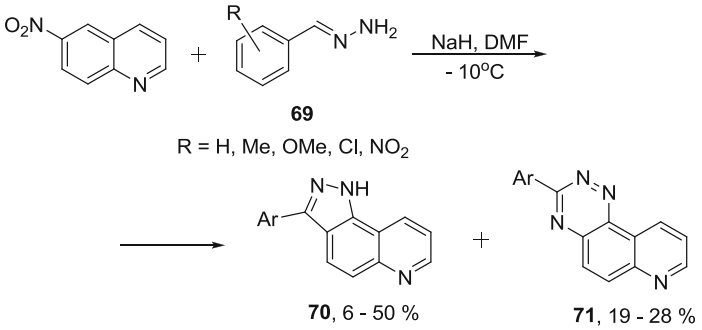
We have established that the starting nitro compound, not air oxygen, is likely to be an oxidizing agent, since these reactions proceed pretty well under inert atmosphere.

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

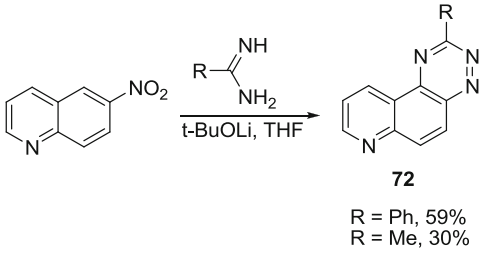
Isomeric triazinoquinolines **72** were synthesized by cyclocondensation of 6-nitroquinoline with amidines [65] (Scheme 35).

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

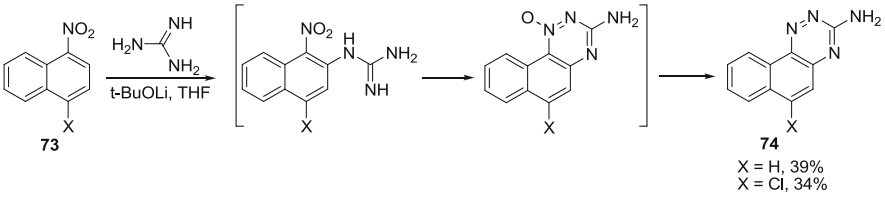
The reaction of 4-substituted 3-fluoronitrobenzenes **75** with guanidine results in the formation of a mixture of isomeric benzotriazines with a predominance of compound **76** [66] (Scheme 37). The first step of this process is likely to be ONS



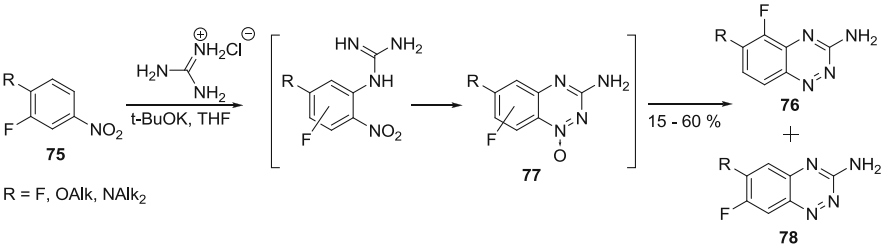
Scheme 34 Synthesis of N-heterocycles from 6-nitroquinoline



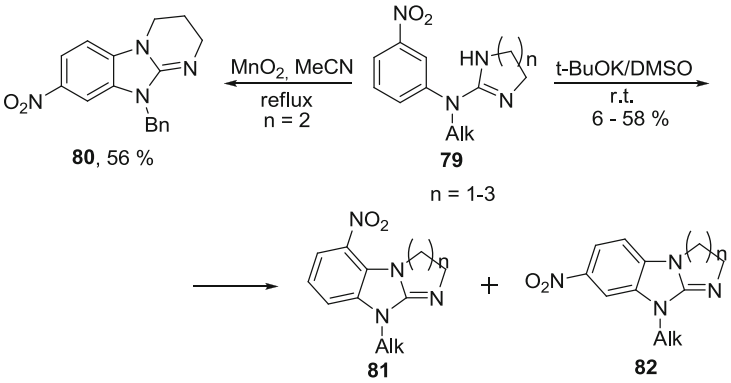
Scheme 35 Synthesis of fused triazinoquinolines from 6-nitroquinoline



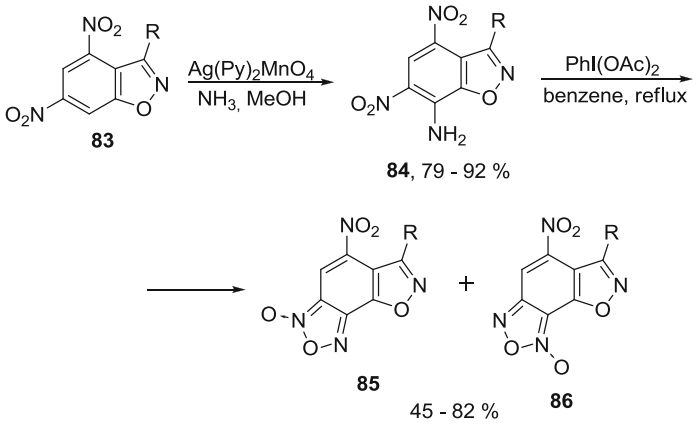
Scheme 36 ONS in nitronaphthalene series leading to naphthotriazines



Scheme 37 Synthesis of benzotriazines



Scheme 38 Synthesis of condensed benzimidazoles through the ONS of hydrogen



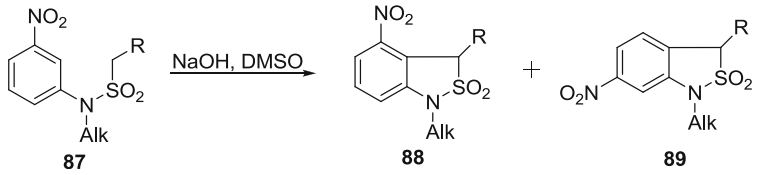
Scheme 39 Oxidative amination and cyclizations of 4,6-dinitrobenzo[*d*]isoxazoles

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

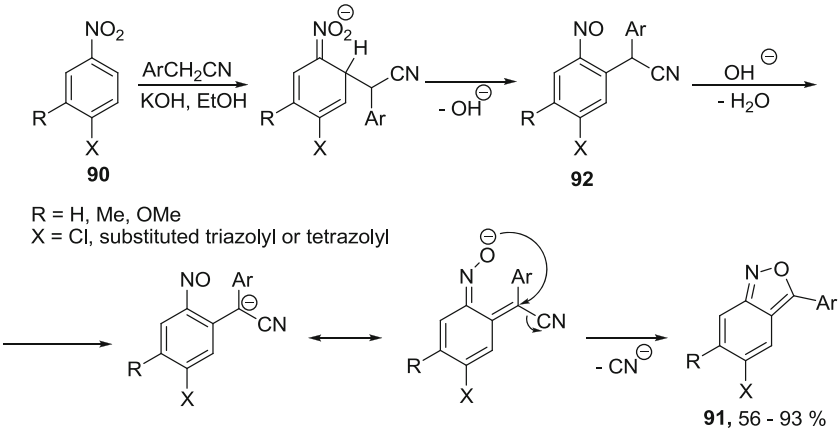
The fused benzimidazoles can also be obtained based on the intramolecular ONS reactions of cyclic guanidines **79** [67] (Scheme 38).

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

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



Scheme 40 Cyclization of *meta*-nitrophenyl substituted sulfonamides



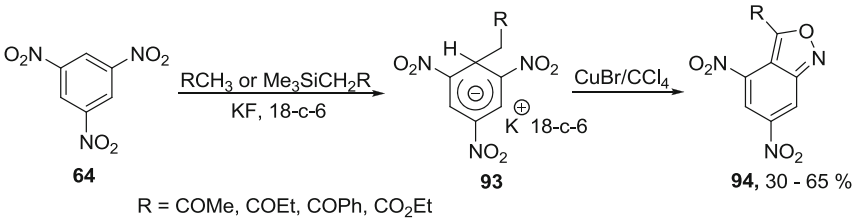
Scheme 41 Synthesis of anthranils through the intramolecular redox process

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

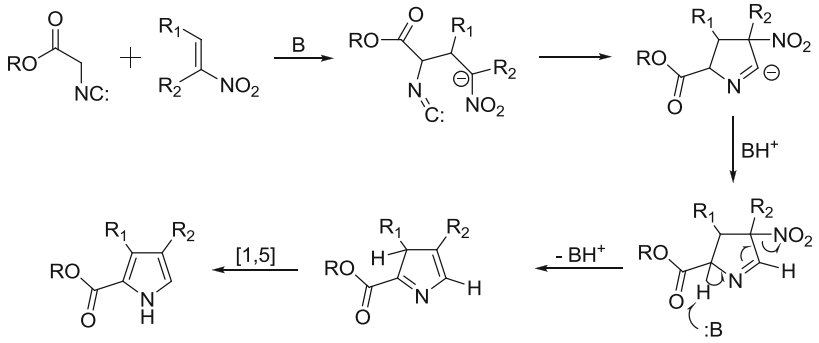
Sometimes the nucleophilic addition at carbon atom of the nitroaromatic ring may cause aromatization to go through transformation of the σ^H-adduct into a nitroso compound (i.e., via intramolecular redox process). In other words, oxidation of σ^H-adduct proceeds due to reduction of the nitro group. The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

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

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



Scheme 42 Oxidation of TNB anionic σ-adducts



Scheme 43 The Barton–Zard reaction (general scheme)

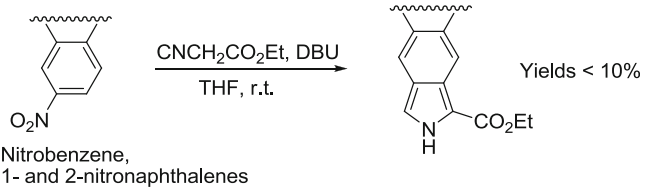
such processes are growing permanently [6, 9, 10, 73]. It undeniably indicates a considerable interest in the S_N^H methodology, which is now widely used in heterocyclic chemistry.

3 Barton–Zard Reaction

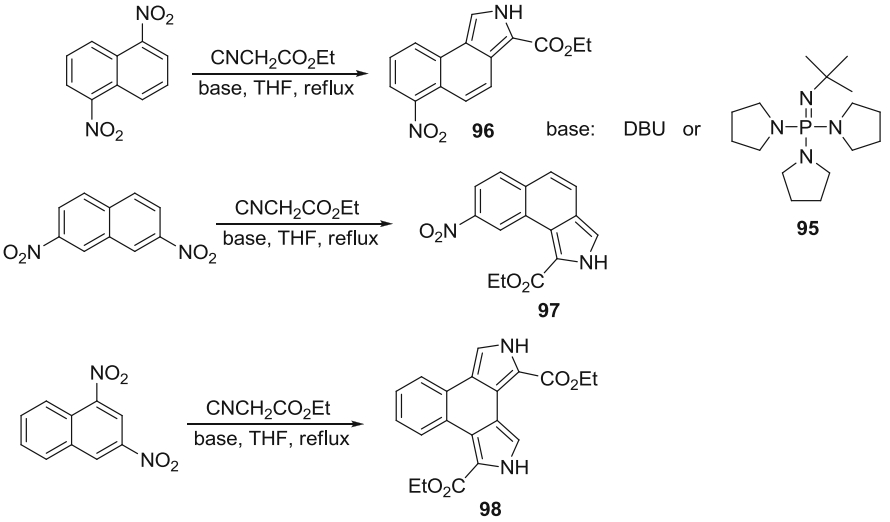
It is a common point of view that the Barton–Zard reaction is a favorable one for the pyrrole synthesis. It is based on interaction of conjugated nitroalkenes with isocyanoacetates in the presence of a base [6, 74–76] and, basically, involves three steps (Scheme 43): the Michael-type addition of isocyanide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

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

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



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



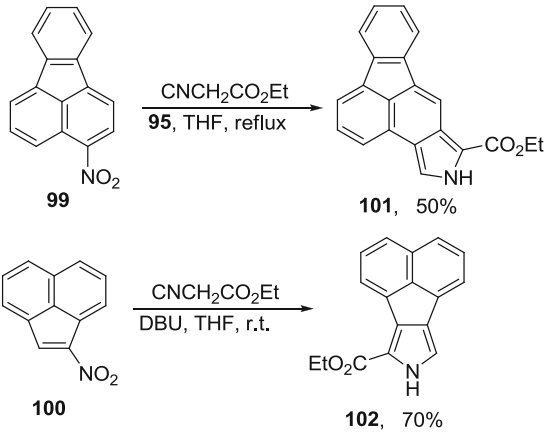
Nitro compound	Product	Yield (with DBU)	Yield (with **95**)
1,5-Dinitronaphthalene	**96**	45	78
2,7-Dinitronaphthalene	**97**	44	71
1,3-Dinitronaphthalene	**98**	25	31

Scheme 45 Synthesis of benzo-fused isoindoles from dinitronaphthalenes

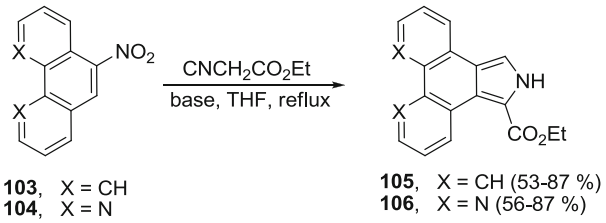
However, nitroaromatic compounds with a profound nitroalkenic character, as well as their dinitro derivatives, proved to undergo the Barton–Zard reaction much easier to give moderate-to-good yields of the target products. Indeed, 1,3-, 1,5-, and 2,7-dinitronaphthalenes gave the corresponding isoindoles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

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

Scheme 46 Annelation of the pyrrole ring to polycyclic aromatics



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



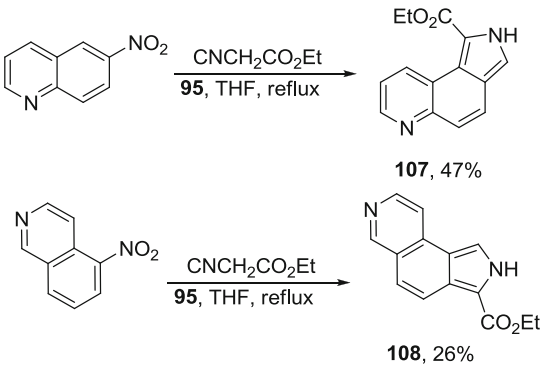
Analogously, nitrophenanthrene and phenanthroline derivatives **103** and **104** (Scheme 47) were transformed into dibenzo- and dipyridinoisoindoles, respectively [77, 81, 84, 85].

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

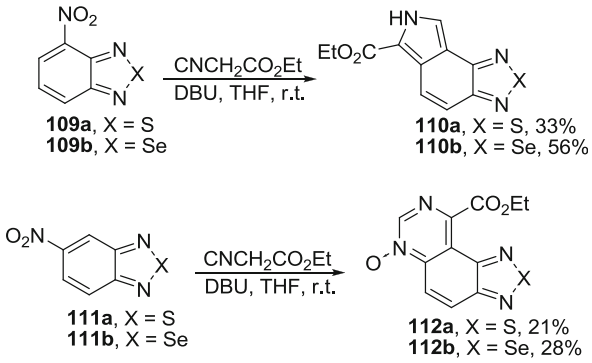
However, the Barton–Zard reaction seems to be rather sensitive to the structure of starting nitroarenes, and depending on position of the nitro group, the reaction results in the formation of various heterocycles. 4-Nitrobenzothia- and selenadiazoles have been shown to react with ethyl isocyanoacetate/DBU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

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

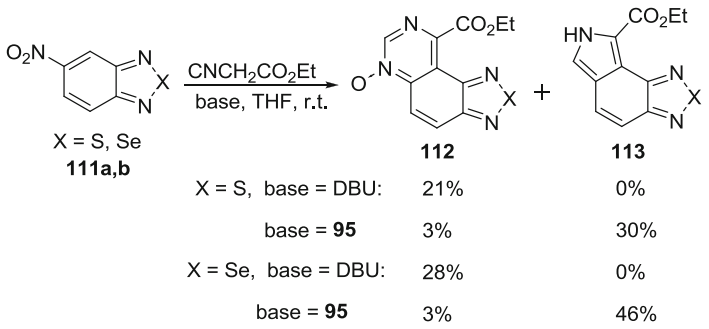
Varying base allows to obtain a wide range of functionalized isoindoles fused with the thiadiazole ring or bearing substituents in the pyrrole ring [88].



Scheme 48 Synthesis of pyridino-annelated isoindoles

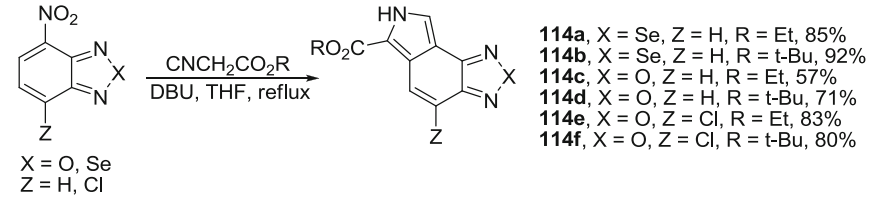


Scheme 49 The Barton–Zard reaction of 4- and 5-nitrobenzoazoles

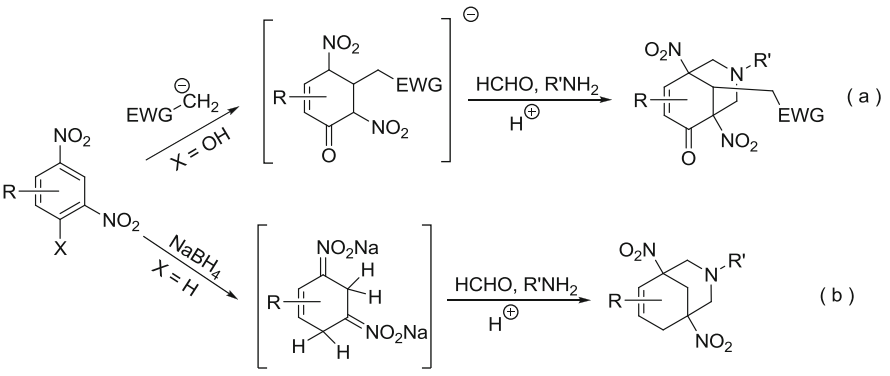


Scheme 50 The Barton–Zard reaction of 5-nitrobenzoazoles

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



Scheme 51 The Barton–Zard reaction of 4-nitrobenzoazoles



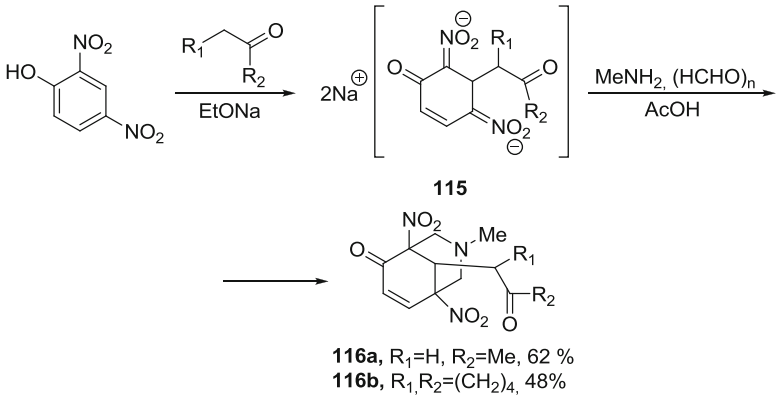
Scheme 52 Formation of anionic adducts of nitroarenes and subsequent Mannich cyclizations

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

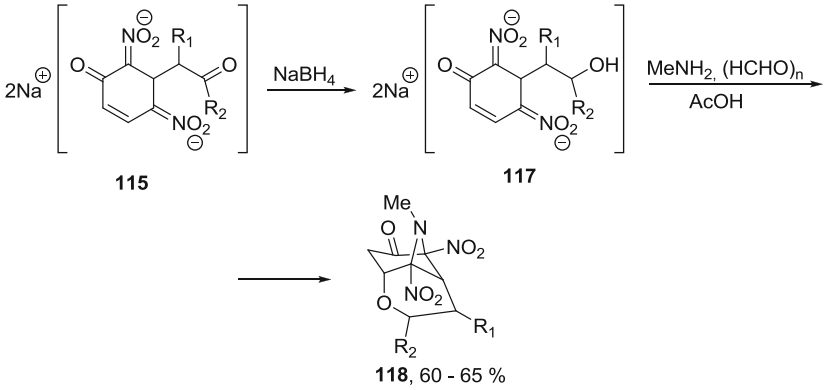
From the data considered above it is clear that the Barton–Zard condensation of nitroarenes is a convenient method for the synthesis of polycyclic compounds of the isoindole family. Formally the reaction involves the S_N^H process and further cyclization into the pyrrole ring accompanied by elimination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

4 Mannich Cyclization of Anionic Adducts of Nitroarenes

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



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

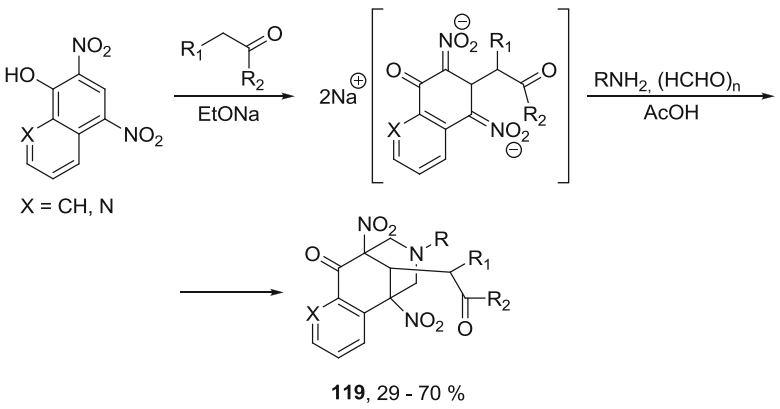


Scheme 54 Cyclization of anionic adducts of nitroarenes

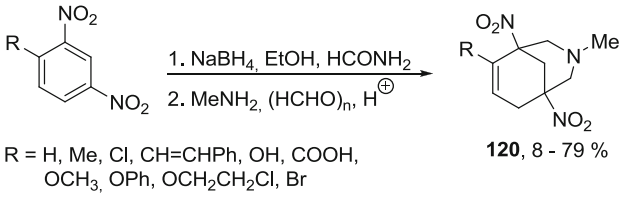
Scheme 53 illustrates the path (a). In one of the pioneer publications on such type of transformations, Severin et al. [90] described the interaction of disodium salt **115** (adduct of 2,4-dinitrophenol and acetone) with methylamine and formaldehyde in the presence of acetic acid. As a result, bicyclic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

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

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



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



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

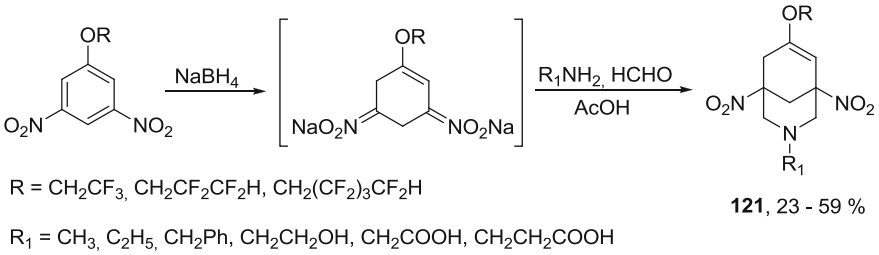
A number of condensed 3-azabicyclo[3.3.1]nonanes **119** were synthesized from 2,4-dinitronaphthol [92, 93] and 5,7-dinitro-8-hydroxyquinoline [94] (Scheme 55).

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

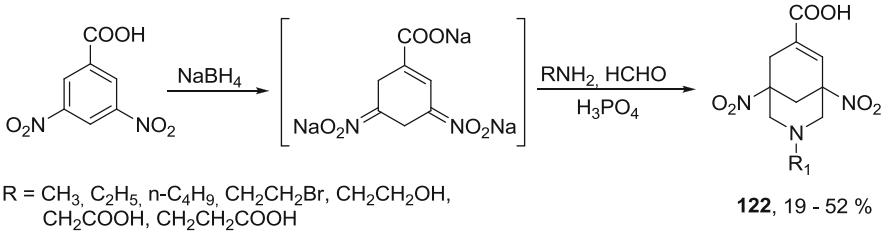
A number of 7-polyfluoroalkoxy 1,5-dinitro-3-azabicyclo[3.3.1]non-6-enes **121** were synthesized by means of reduction of polyfluoroalkyl ethers of 3,5-dinitrophenol with sodium borohydride followed by the Mannich reaction with formaldehyde and alkyl amines [98] (Scheme 57).

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

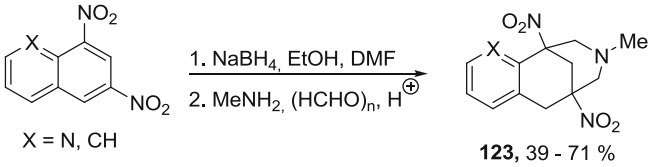
meta-Dinitronaphthalene and its quinoline analogue have been shown to react smoothly with $NaBH_4$, followed by cyclization into 3-azabicyclo[3.3.1]nonanes **123** fused with the benzene or pyridine ring, respectively [100] (Scheme 59).



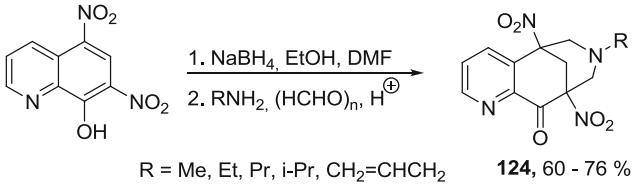
Scheme 57 Synthesis of polyfluoroalkoxy 1,5-dinitro-3-azabicyclo[3.3.1]non-6-enes



Scheme 58 Cyclization of the hydride adducts



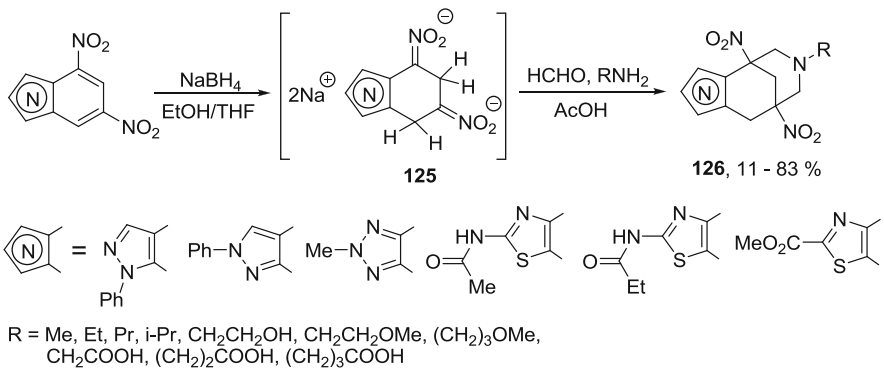
Scheme 59 Bicyclic nitroarenes as precursors of fused 3-azabicyclo[3.3.1]nonanes



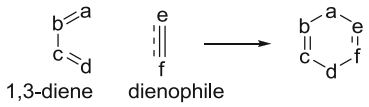
Scheme 60 Synthesis of 3-azabicyclo[3.3.1]nonanes fused with the pyridine ring

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

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



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



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

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

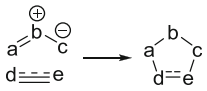
5 Pericyclic Reactions of Nitroarenes

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

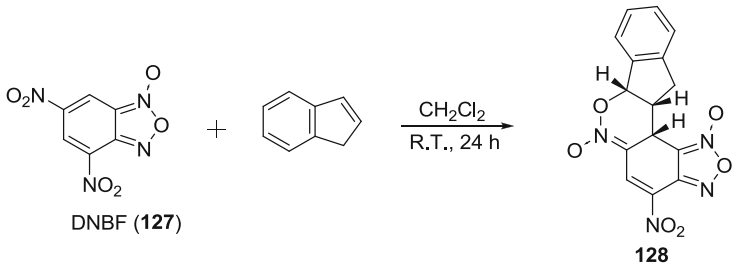
The [4+2]-cycloaddition reactions lead to the formation of six-membered rings through interaction of conjugated 1,3-dienes (4π system) with alkenes and acetylenes (dienophiles, 2π system) [108] (Scheme 62).

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

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



Scheme 63 [3+2] Cycloaddition reaction



Scheme 64 Reaction of DNBF with indene

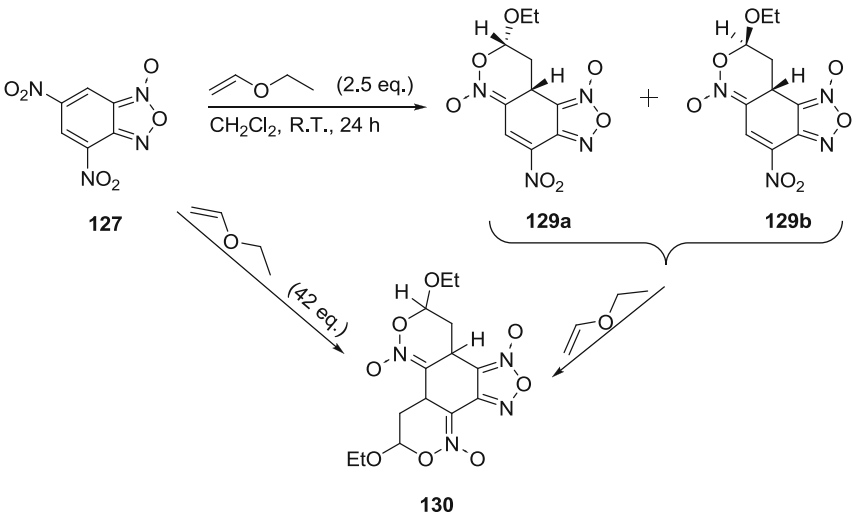
as heterodienophiles, such as –C=N, –C=O, –C=S, –N=N–, –S=O, and –N=O, can also undergo [4+2]-cycloaddition reactions to give six-membered heterocycles. [4+2] Cycloaddition appears to be one of the most widely applied reactions in organic chemistry [106, 108–110]. It is used for the synthesis of various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

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

5.1 [4+2]-Cycloaddition Reactions

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

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



Scheme 65 DNBF as heterodiene in the Diels–Alder reaction

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

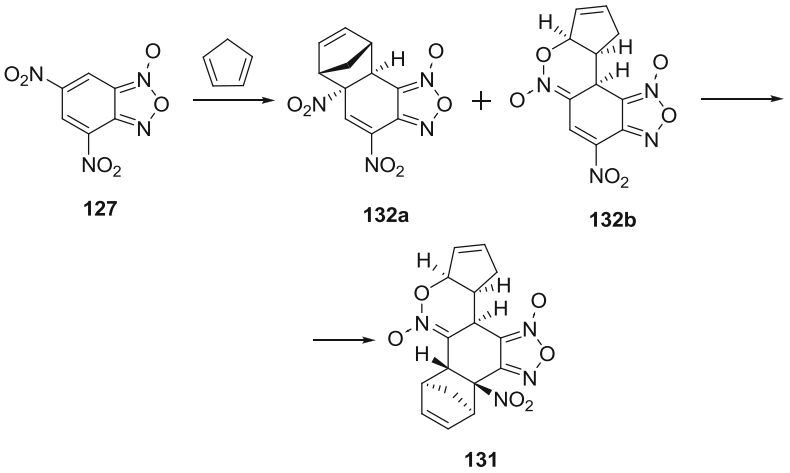
When ethyl vinyl ether was used as solvent, a mixture of several diastereomeric *bis*-adducts **130** was obtained [116]. Stereochemical features for the major products have been studied, and the reaction mechanism proved to be in agreement with an inverse electron demand cyclization.

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

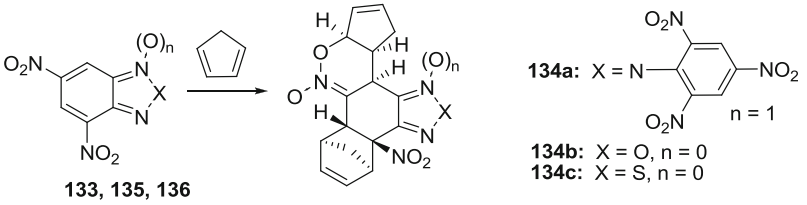
Use of ^{1}H NMR spectroscopy revealed that, at a low reaction temperature (−30°C), the adducts **132a**,**b** are initially formed, which then react subsequently upon a gradual increase of temperature into polycyclic compound **131** (Scheme 66). It is clear that at the initial step there are two competing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

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

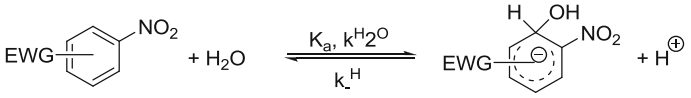
4,6-Dinitrobenzofurazan (**135**) and 4,6-dinitrobenzothiadiazole (**136**) behave similarly [119] (Scheme 67) and are capable of reacting with cyclopentadiene into *bis*-adducts **134b**,**c** in 68% and 32% yields, respectively. It is worth noting that 4,6-dinitrobenzoselenadiazole (X = Se, n = 0)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



Scheme 66 Cycloadducts derived from the reaction of DNBF with cyclopentadiene



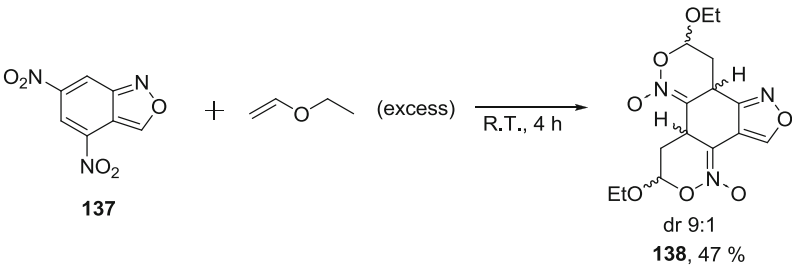
Scheme 67 4,6-Dinitrobenzoazoles as dienophiles and heterodienes



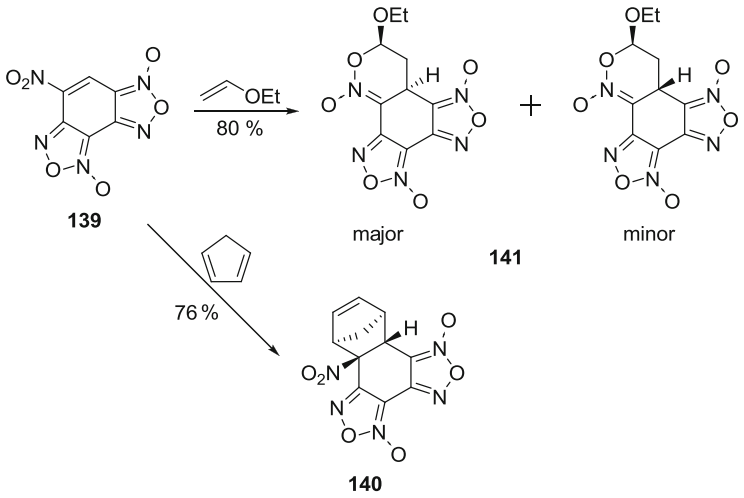
Scheme 68 Equilibrium for the σ^H-adducts formation

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

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



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

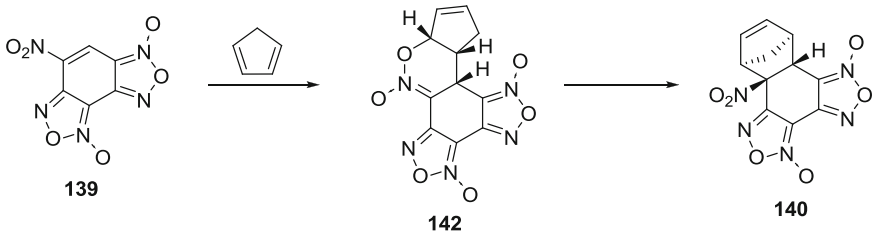


Scheme 70 NBDF as dienophile and heterodiene

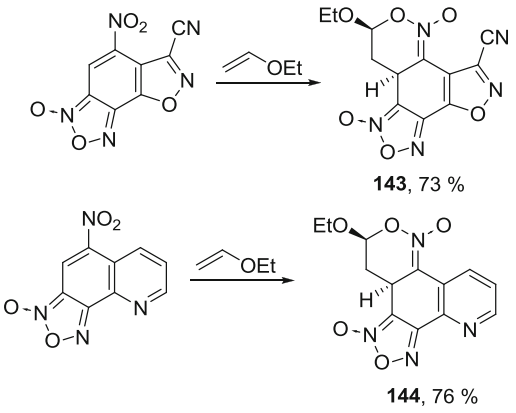
Kurbatov et al. [122] studied properties of 4-nitrobenzodifuroxan **139** (NBDF) and found that, in spite of the formal aromatic structure, the C=C–NO_2 fragment has pronounced nitroalkene character. NBDF was found to undergo cycloaddition with dienes (in accord with NED), and, as a heterodiene, it is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

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

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



Scheme 71 The formation of NBDF-cyclopentadiene adducts



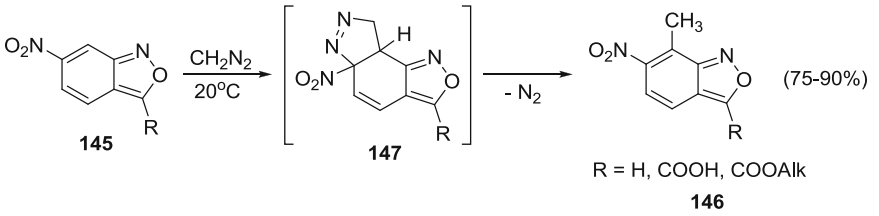
Scheme 72 Synthesis of cyclic nitronates via the Diels–Alder reaction of nitroarenes

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

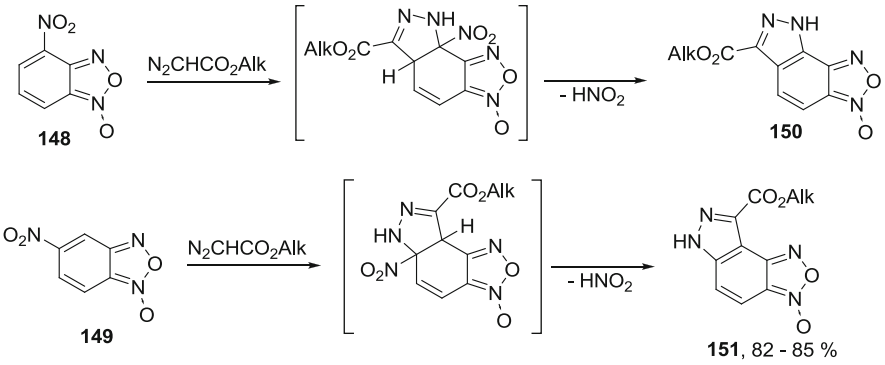
5.2 [3+2]-Cycloaddition Reactions

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

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



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



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

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

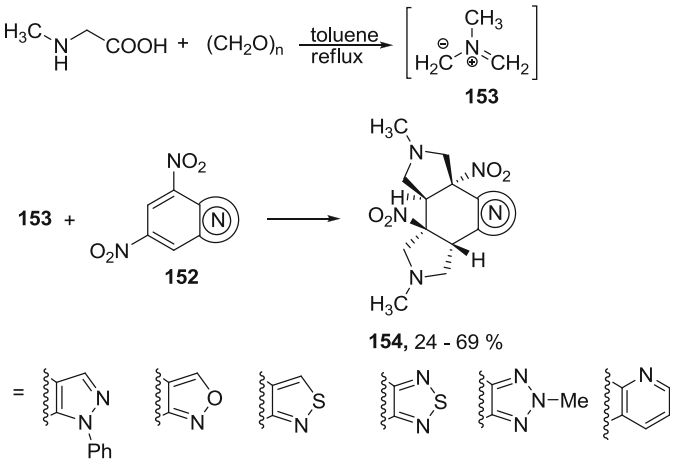
Although the intermediate [3+2] cycloadducts **147** have neither been registered nor isolated, Chandra Boruah et al. [127] claim that these intermediates can be detected chromatographically at a low temperature.

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

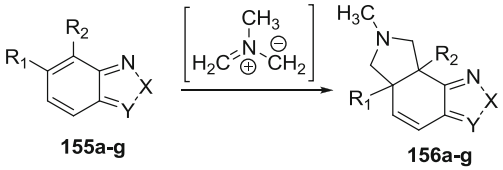
During the last decade we have been carrying out a systematic study of the reactions of nitroarenes with N-alkyl azomethine ylides. A fundamentally new approach has been advanced for the synthesis of polycyclic heterosystems bearing important pharmacophoric fragments, such as pyrrolidines, pyrrolines,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

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

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



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

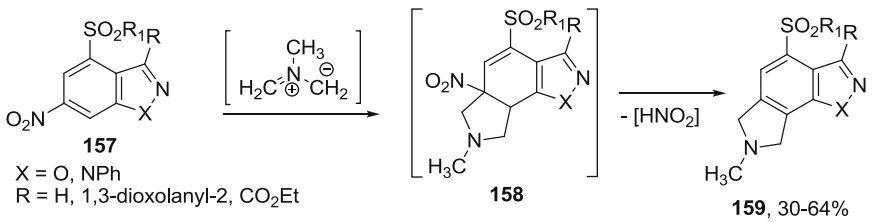


Compound	X	Y	R_1	R_2	Product	Yield (%)
155a	O	N	H	NO_2	**156a**	75
155b	S	N	H	NO_2	**156b**	42
155c	Se	N	H	NO_2	**156c**	46
155d	O	CH	NO_2	H	**156d**	40
155e	O	N	NO_2	H	**156e**	98
155f	S	N	NO_2	H	**156f**	64
155g	Se	N	NO_2	H	**156g**	47

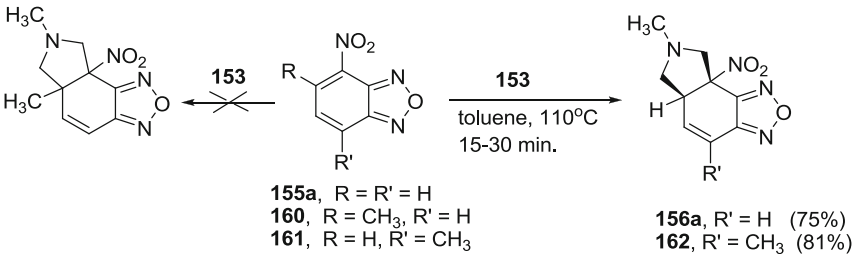
Scheme 76 Synthesis of tetrahydroisoindoles fused with azoles

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

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



Scheme 77 Synthesis of isoindolines fused with azoles



Scheme 78 Synthesis of tetrahydroisoindoles fused with furazan

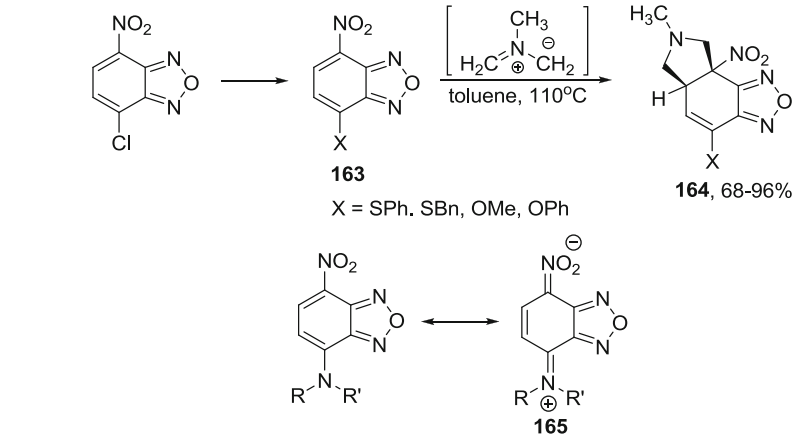
Sulfonyl derivatives **157** containing one nitro group behave analogously (Scheme 77). However, the intermediate cycloadducts **158** undergo aromatization under the reaction conditions, with the loss of nitrous acid.

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

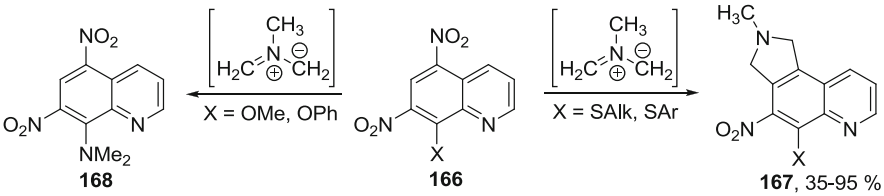
At the same time, isomeric 7-methyl-4-nitrobenzofurazan **161** proved to react with N-methyl azomethine ylide **153** in a similar to benzofurazan **155a** manner to give tetrahydroisoindole **162** in a high yield (Scheme 78).

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

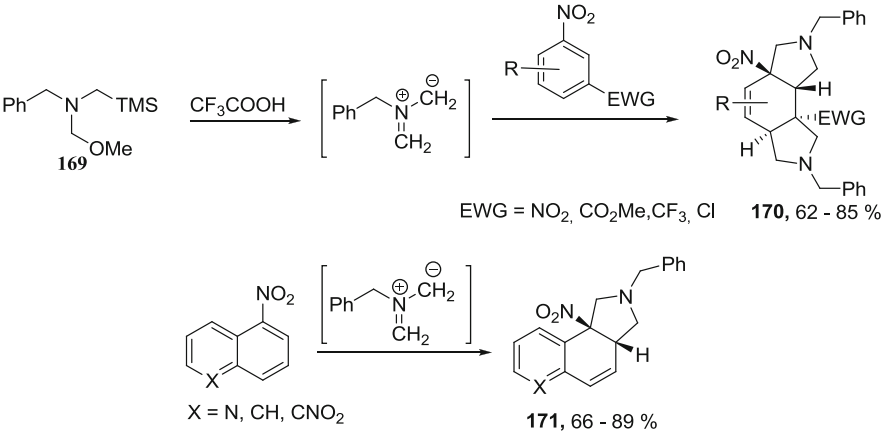
8-X-5,7-Dinitroquinolines **166** are also able to react with dipole **153** (Scheme 80). However, in this particular case, the reaction is governed by the nature of substituent X in position 8 [133]. 8-SR-Derivatives undergo the addition of this dipole exclusively across the C(5)–C(6) bond to give pyrrolines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



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

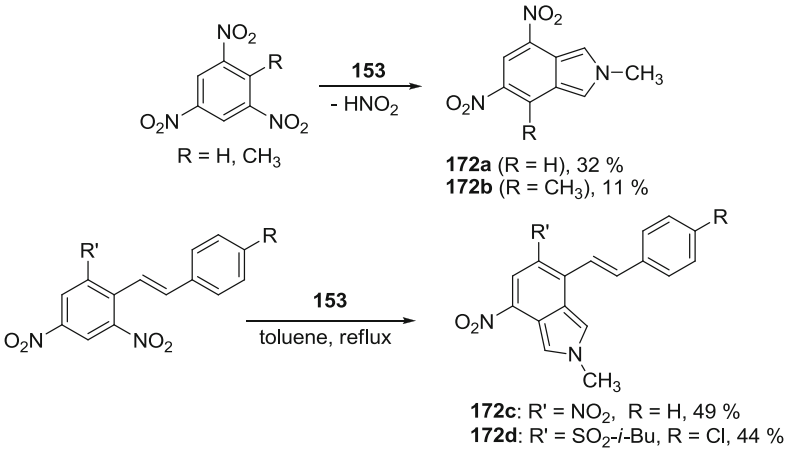


Scheme 80 Synthesis of isoindolines fused with the pyridine ring



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

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



Scheme 82 Synthesis of functionalized isoindoles

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

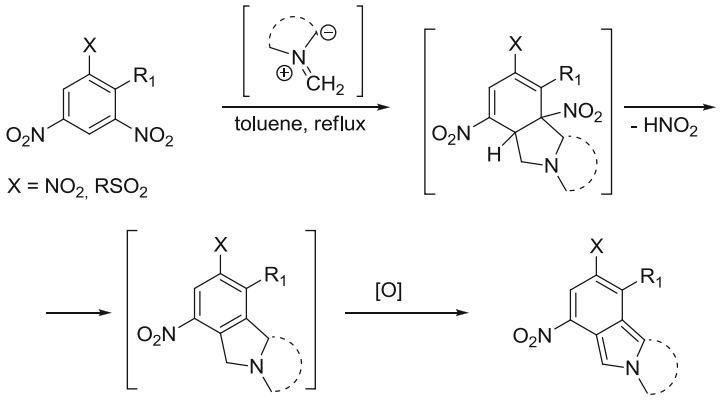
In continuation of our systematic studies, we have investigated the reactions of substituted di- and trinitrobenzenes with a series of N-alkyl azomethine ylides [135]. It has been found that 1,3-di- and 1,3,5-trinitrobenzenes react with N-methyl azomethine ylide (**153**) to give isoindoles **172** in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

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

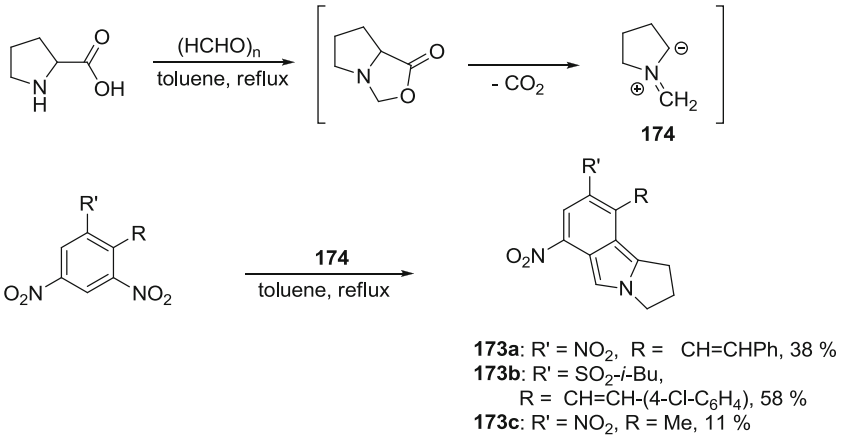
Although these reactions were carried out in the presence of air oxygen, nitroaromatic substrates were likely to be oxidizing agents, since yields proved to be the same in inert atmosphere. Furthermore, it should be noted that, in case of monocyclic di- and trinitrobenzenes, the dipole adds only across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

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

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

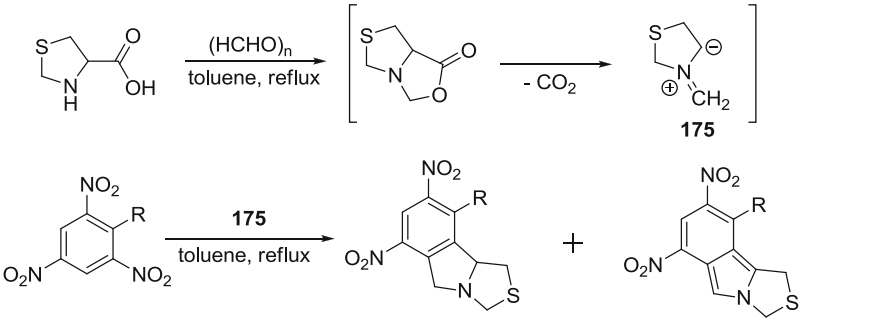


Scheme 83 Cycloaddition of N-alkyl azomethine ylides with polynitrobenzenes



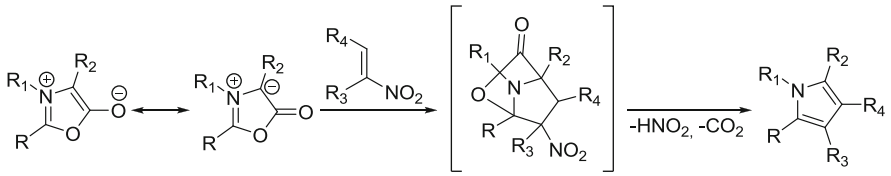
173a: R' = NO_2, R = CH=CHPh, 38 %
173b: R' = SO_2-*i*-Bu,
R = CH=CH-(4-Cl-C_6H_4), 58 %
173c: R' = NO_2, R = Me, 11 %

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

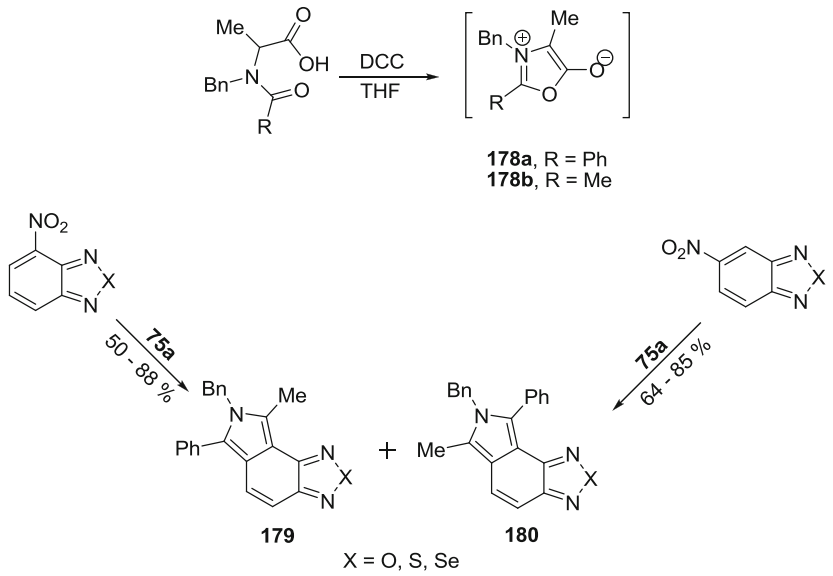


176a, R = CH_3, 34 %
176b, R = CH=CHC_6H_5, 36 % **177b,** R = CH=CHC_6H_5, 35 %

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



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

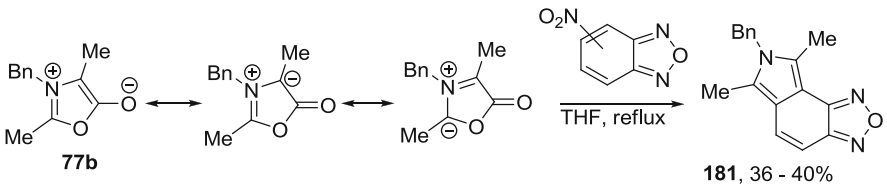


Scheme 87 1,3-Dipolar cycloaddition of münchnones to nitrobenzoazoles

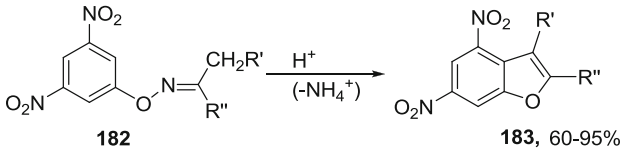
One more example of 1,3-dipolar cycloaddition with nitroarenes is the reaction of nitrobenzazoles with mesoionic 1,3-oxazolium-5-olates (münchnones) [136]. Münchnones are known to react as 1,3-dipoles with conjugated nitroalkenes [137] and some nitroheterocyclic compounds [138]. The münchnone molecule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

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

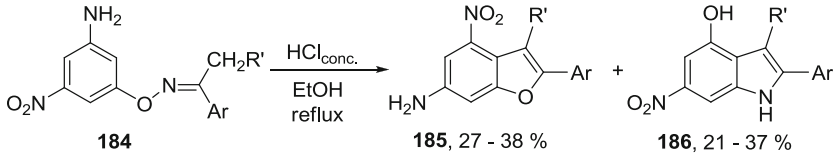
Each isomer can be isolated, using flash chromatography. In case of 2,4-dimethyl münchnone **178b** the reactions with 4- or 5-nitrobenzofurazans gave the same isoindole **181** (Scheme 88).



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



Scheme 89 Cyclization of *O*-dinitrophenyl oximes



Scheme 90 Synthesis of 4-hydroxy-6-nitroindoles

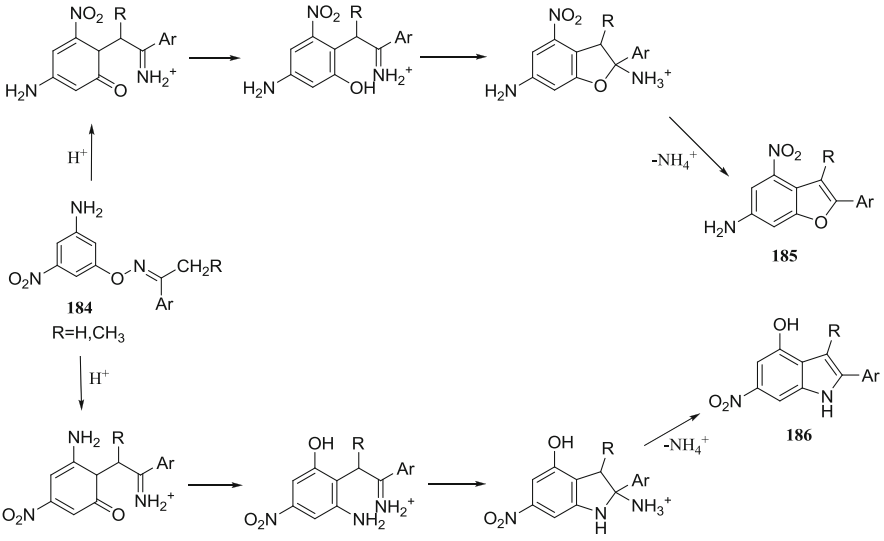
In summary, we have succeeded in developing a novel one-step method for the synthesis of isoindoles by annelation of the pyrrole ring to the benzene ring of nitroarenes.

6 Other Transformations

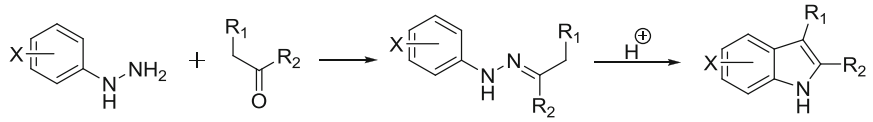
Aside from chemical transformations described above, there are some other approaches to the synthesis of nitrogen heterocycles using CH-functionalization of nitroarenes; among them an acid-promoted cyclization of *O*-nitrophenyl ketoximes **182** appears to be of particular interest [139] (Scheme 89).

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

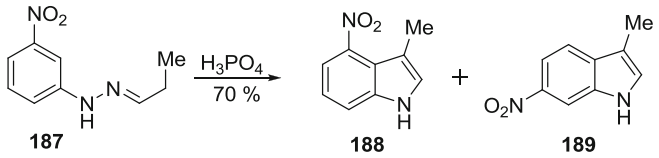
The authors suggested a plausible reaction scheme (Scheme 91) explaining the formation of both types of heterocycles.



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



Scheme 92 The Fisher indole synthesis

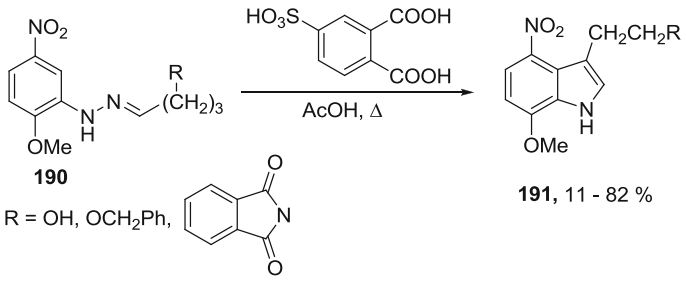


Scheme 93 Synthesis of isomeric nitroindoles

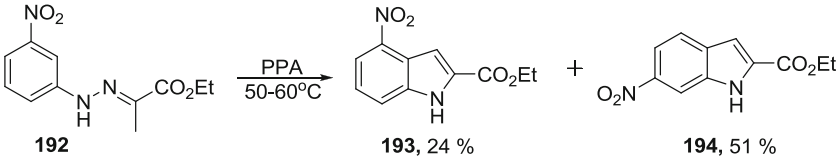
Another approach to N-heterocycles on the basis of nitroarenes is represented by cyclization of nitroaryl-substituted hydrazones of carbonyl compounds into indoles (Fisher indole synthesis) [141] (Scheme 92).

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

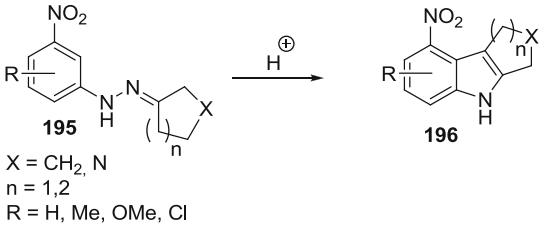
For example, heating 3-nitrophenyl hydrazone of propioaldehyde **187** in a mixture of toluene – 85% orthophosphoric acid gave rise to a hardly separable mixture of two regioisomers **188** and **189** (Scheme 93) in 70% overall yield [142].



Scheme 94 Synthesis of 4-nitroindoles



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



Scheme 96 Synthesis of condensed nitroindoles

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

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

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

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

7 Conclusion

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

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C–H Functionalization of Heteroaromatic *N*-Oxides

Yoshinori Kondo

Abstract Heteroaromatic *N*-oxides have received wide attention as useful synthetic intermediates, various functional molecules, and biologically active compounds. On the other hand, C–H functionalization of heteroaromatic *N*-oxides is one of the key methods of organic synthesis for selectively introducing substituents in heteroaromatic rings. Organometallic chemistry has played an important role in selective transformation of organic molecules, but recently developed metal-free processes are regarded as attractive methodologies from a viewpoint of environmentally benign organic synthesis. Recent advances in the field of nucleophilic C–H functionalization of heteroaromatic *N*-oxides using metal-free processes are discussed.

Keywords Benzyne · C–H functionalization · Heteroaromatic *N*-oxides · Metal-free reactions · Nucleophilic addition · Organocatalyst · Radical reactions

Contents

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1 Introduction

Heteroaromatic *N*-oxides have received wide attention as useful synthetic intermediates, catalysts, oxidants, and ligands [1–7]. Some compounds are known to have important biological or pharmaceutical activities [8]. In this review, metal-free methodologies for functionalization of heteroaromatic *N*-oxides are the main subject to be discussed, but the metal-free reactions are closely related to organometallic methodologies, and they both are considered to be complementary with each other in organic synthesis. Before starting the discussion on metal-free processes, recent advances in organometallic C–H functionalizations of heteroaromatic *N*-oxides are overviewed in the introduction.

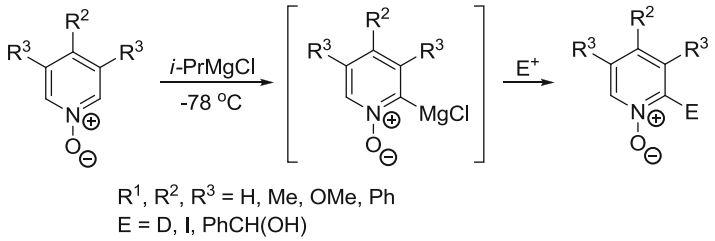
Direct metalation of a heteroaromatic ring has been achieved using organolithium, organomagnesium, and organozinc compounds. Use of organolithium reagents for deprotonation of pyridine *N*-oxides followed by addition of electrophiles has been studied, and so far only poor to moderate yields of 2-substituted pyridines have been reported along with 2,6-disubstituted pyridines as major by-products [9–12].

A mild and convenient method was developed for the selective C–H functionalization leading to 2-substitution of hydrogen in pyridine *N*-oxides via a directed *ortho*-magnesiation using *i*-PrMgCl (Scheme 1). The generated magnesio intermediates were trapped successfully with various electrophiles, ranging from aldehydes and ketones to halogens [13]. By applying a transition metal-catalyzed cross-coupling, the direct arylation of pyridine *N*-oxides was also achieved.

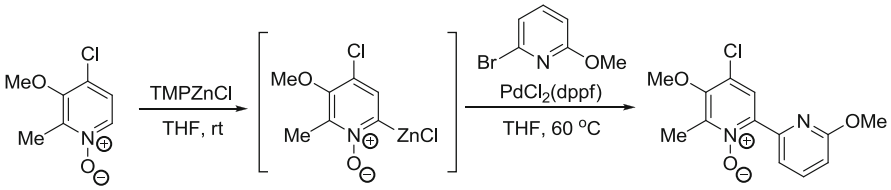
Substituted pyridine *N*-oxides are able to undergo a highly regioselective zincation with TMPZnCl-LiCl under rather mild reaction conditions (Scheme 2). A palladium-catalyzed Negishi cross-coupling reaction of the resulting organozinc species with heteroaromatic bromides provides heterobiaryls specially oxidized at one nitrogen position in high yield [14]. Recent advances in C–H magnesiation and zincation of heteroaromatic compounds have been well described in the review articles by Knochel and co-workers [15, 16].

Palladium-catalyzed direct arylations were reported with a broad range of heteroaromatic *N*-oxides (Scheme 3) [17]. In addition to aspects of functional group compatibility, the issues of regioselectivity have also been explored for those reactions in which nonsymmetrical heteroaromatic *N*-oxides are used. In these cases, both the choice of ligand and the nature of heteroaromatic substituents play important roles in determining the regioisomeric distribution. Palladium-catalyzed direct arylation of pyridine *N*-oxides followed by a catalytic reduction with ammonium formate results in the formation of 2-arylpyridines in good to high yields based on the aryl bromide; however, 4 equiv. of the starting pyridine *N*-oxide was used for the completion of the reaction. The potential utility of this methodology was illustrated by its use for the synthesis of potent sodium channel inhibitor 1 [18] and a Tie2 tyrosine kinase inhibitor 2 [19].

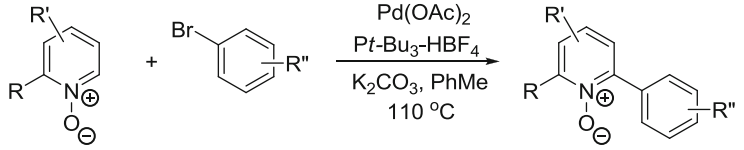
Substituted bipyridines were efficiently prepared by direct coupling between pyridine *N*-oxides and halopyridines using a palladium catalyst (Scheme 4) [20]. It is worth noting that pyridine *N*-oxides bearing electron-withdrawing substituents



Scheme 1 C–H functionalization of pyridine *N*-oxides through deprotonative magnesiation



Scheme 2 C–H functionalization of pyridine *N*-oxides through deprotonative zincation



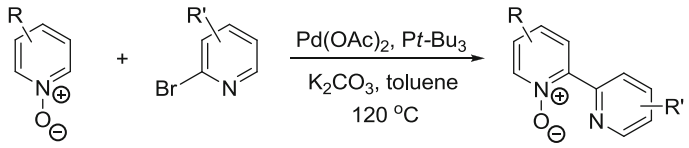
Scheme 3 Palladium-catalyzed arylation of pyridine *N*-oxides

gave the best yields. This method allows a convenient way for preparation of 2,2′-, 2,3′-, and 2,4′-bipyridines which are useful as functionalized ligands for metal complexes or as building blocks for supramolecular architecture.

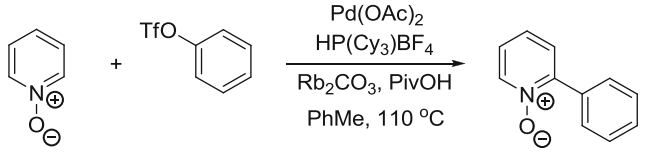
Palladium-catalyzed direct arylation of heteroaromatic *N*-oxides using aryl triflates was reported to afford the corresponding 2-aryl heteroaromatic *N*-oxides (Scheme 5) [21]. The reaction was carried out with a range of both azine *N*-oxides and aryl triflates. The arylation can also be carried out as a sequence of reactions to yield various diarylated products. The regioselectivity and scope for the direct arylation of 3-substituted azine *N*-oxides have been investigated. The method can be applied for the synthesis of compounds that exhibit antimalarial [22] and antimicrobial [23] activities.

The direct arylation of electron-deficient heteroaromatic *N*-oxides with aryl and alkenyl tosylates or mesylates was achieved by using a palladium catalyst (Scheme 6) [24].

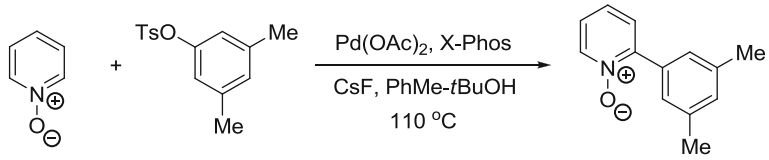
The Pd(II)-catalyzed oxidative coupling reaction between pyridine *N*-oxides and *N*-substituted indoles, which involves activation of two C–H bonds, in both



Scheme 4 Palladium-catalyzed synthesis of bipyridine *N*-oxides



Scheme 5 Arylation of pyridine *N*-oxides using aryl triflates



Scheme 6 Arylation of pyridine *N*-oxides using aryl tosylates

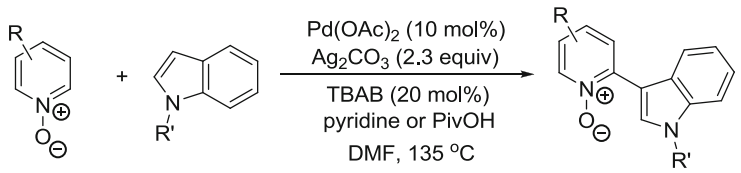
substrate and reagent, has been achieved with high selectivity, by using Ag_2CO_3 as oxidant (Scheme 7) [25].

It was also reported that the use of quinoxaline *N*-oxide gives rise to coupling in even a higher yield than the parent indole-pyridine coupling reaction (Scheme 8) [26]. The coupling reactions with isoquinoline, phthalazine, and pyrimidine *N*-oxides proved to proceed smoothly, and their regioselective outcomes were found to be consistent with the parent coupling reaction.

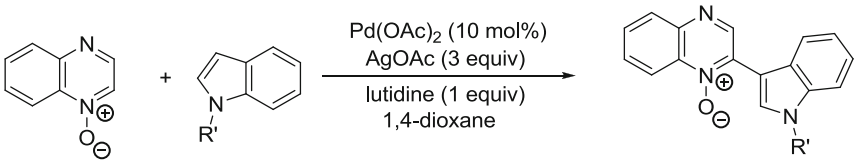
Nickel-catalyzed activation of the C(2)-H bond in pyridine *N*-oxides allowed the latter to react with alkynes under mild conditions to afford (*E*)-2 alkenylpyridine *N*-oxides in modest to good yields (Scheme 9) [27]. The compounds obtained can be deoxygenated readily to give various substituted pyridines, which are regarded as useful intermediates for pharmaceuticals and materials.

A highly efficient and convenient rhodium catalytic system was developed for the direct hydroheteroarylation of unsaturated compounds with heteroarenes (Scheme 10) [28]. A base cocatalyst was found to be crucial for the heteroarene C–H activation step. Substrate scope was very broad, including both electron-deficient pyridine *N*-oxides and electron-rich azoles. The identical catalytic system was found to be appropriate for hydroheteroarylation of both alkenes and alkynes with excellent regioselectivity and stereoselectivity.

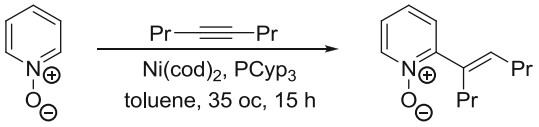
Also Cu-catalyzed C–C coupling of 2-phenylpyridine *N*-oxide with internal secondary allyl phosphates was found to proceed under mild reaction conditions with excellent γ and E-selectivities (Scheme 11) [29].



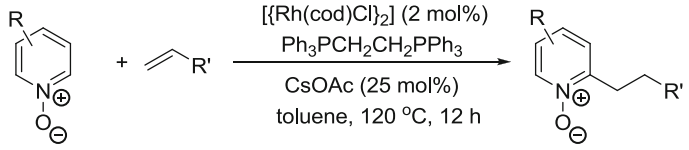
Scheme 7 Coupling of pyridine *N*-oxides with *N*-substituted indoles



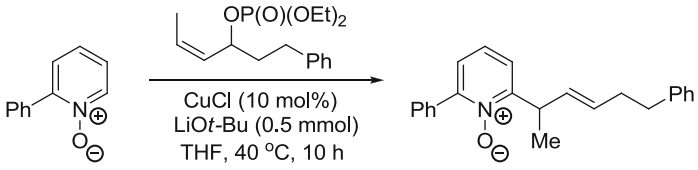
Scheme 8 Coupling of quinoxaline *N*-oxide with *N*-substituted indoles



Scheme 9 Nickel-catalyzed alkenylation of pyridine *N*-oxide using alkynes

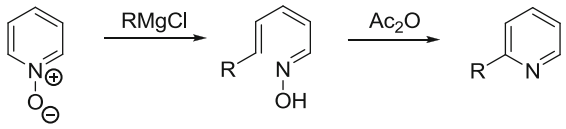


Scheme 10 Rhodium-catalyzed hydroarylation of alkenes with pyridine *N*-oxides



Scheme 11 Copper-catalyzed allylation of pyridine *N*-oxides

The deoxygenative C–H functionalization of heteroaromatic *N*-oxides using Grignard reagents has been investigated by various researchers (Scheme 12). Colonna published the first report on the reaction between pyridine *N*-oxide and Grignard reagents in 1936, in which it was stated that the reaction yielded 2-phenylpyridine when PhMgCl was reacted with pyridine *N*-oxide in diethyl ether [30]. However, Kato



Scheme 12 Deoxygenative C–H functionalization of pyridine *N*-oxides by action of the Grignard reagents followed by treatment with acetic anhydride

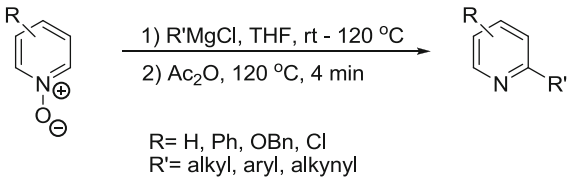
and Yamanaka reinvestigated this reaction in 1965; however, they isolated 1,2-dihydropyridine, instead of the previously reported 2-phenylpyridine [31]. Kellog and van Bergen elucidated the structural aspects of the reaction in 1971, but in contrast to earlier reports, it was found that the reaction gave neither 2-phenylpyridine nor 1,2-dihydropyridine. Instead of it, they isolated the ring-open dienal-oxime [32]. The structure of the ring-open product was confirmed later by Schiress and Ringele [33]. After these publications, which have contributed greatly to understanding of its mechanism, the reaction of pyridine *N*-oxides with the Grignard reagents has been appreciated as an effective method for introducing carbon functionalities at the α position of the pyridine ring. It has been shown by many researchers that sequential addition of the Grignard reagents to pyridine *N*-oxides followed by treatment of the intermediary 2,4-dienal oximes with acetic anhydride affords a range of 2-substituted pyridines in good to high yields (for review, see [34]).

Indeed, the addition of the Grignard reagents to pyridine *N*-oxides in THF at room temperature followed by treatment with acetic anhydride at 120 °C affords 2-substituted pyridines in good to high yields (Scheme 13) [35].

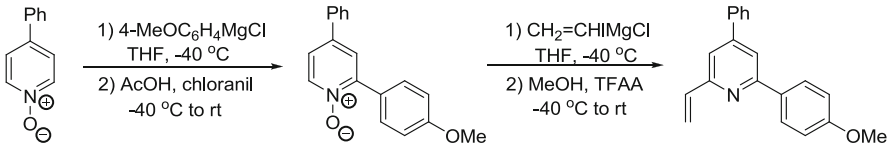
It is worth noting that the addition of the Grignard reagents to pyridine *N*-oxides in THF at low temperature (from −78 to −20 °C) and treatment with trifluoroacetic anhydride (TFAA) provide an efficient general procedure for the synthesis of substituted pyridines (Scheme 14). The method is compatible with a range of functional groups, such as esters, halogens, and nitriles [36].

A new approach to functionally substituted nitroxides has recently been developed based on using the S_N^H reaction [37] of azine *N*-oxides with the lithium salt of nitronyl nitroxide (Scheme 15) [38].

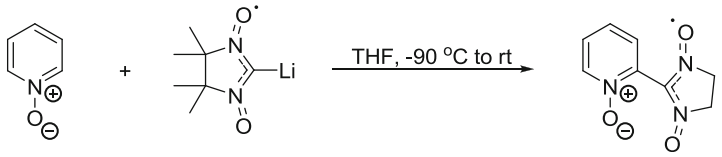
The examples of direct nucleophilic C–H fictionalizations of pyridine *N*-oxides given above (Schemes 13, 14, and 15) illustrate nicely that the reactions of heteroaromatic *N*-oxides with nucleophiles are of great interest and important, differing significantly from those of neutral heteroaromatic base and their onium salts. A great variety of reactions dealing with metal-free C–H functionalization of heteroaromatic *N*-oxide have been developed, and the recent progress will be discussed in the following sections, mainly focusing on publications of the last decade.



Scheme 13 Synthesis of 2-substituted pyridines by using the Grignard reagents



Scheme 14 Synthesis of substituted pyridines by using the Grignard reagents

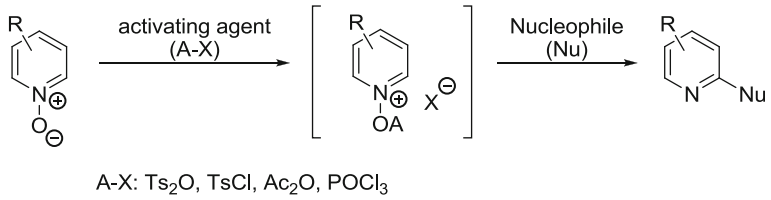


Scheme 15 Reaction of pyridine *N*-oxide with lithium nitronyl nitroxide

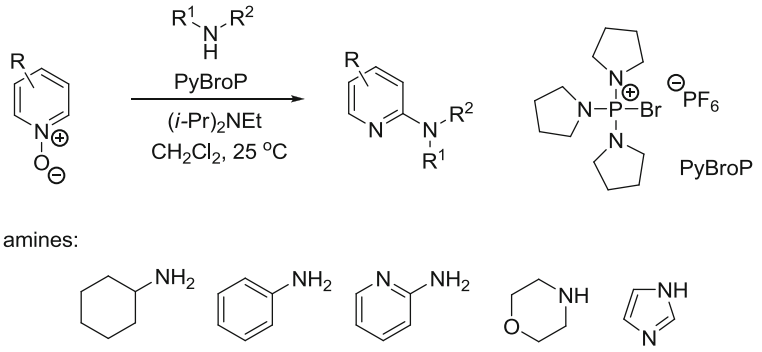
2 Metal-Free C–H Functionalization with Heteroatom Nucleophiles

Two-substituted pyridines feature a structural unit containing in many small molecule compounds, which are of interest for material and medicinal research. A common method for their preparation is the displacement of halogen in the corresponding 2-halopyridines by action of nucleophiles. As a rule, yields for these transformations of inactivated 2-halopyridines are known to be low, and in most cases they require metal catalysis and drastic reaction conditions, such as a high temperature.

Another approach to 2-substituted pyridines is transformation of pyridine *N*-oxide with an activating agent, which enhances the electrophilic character of the 2-position, thus allowing to realize a nucleophilic addition under relatively mild conditions (Scheme 16). In this approach, several side reactions are commonly to occur, including addition at the 4-position, addition of the counter anion at 2 and 4 positions, as well as the direct reaction between activating agent and nucleophile. For these reasons, the development of general, mild, and selective methods for preparation of 2-substituted pyridines has been a challenging task for organic chemists [39–42].



Scheme 16 Nucleophilic C–H functionalization of pyridine *N*-oxides



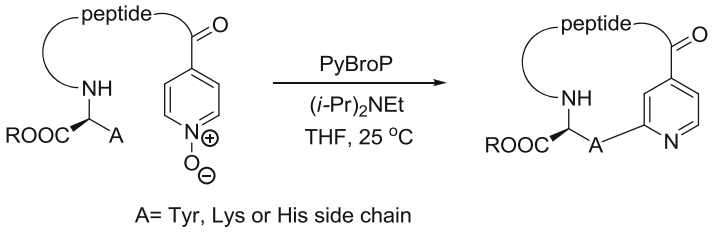
Scheme 17 Amination of pyridine *N*-oxides

Indeed, a general and facile one-pot procedure has been developed for the synthesis of 2-substituted pyridines from the corresponding pyridine *N*-oxides and nucleophiles as a good alternative to S_NAr chemistry. A variety of nucleophiles and heteroaromatic *N*-oxides can participate in this reaction, proceeding effectively in the presence of PyBroP (bromo-*tris*-pyrrolidino-phosphonium hexafluorophosphate), the excellent agent for substrate activation (Scheme 17) [43].

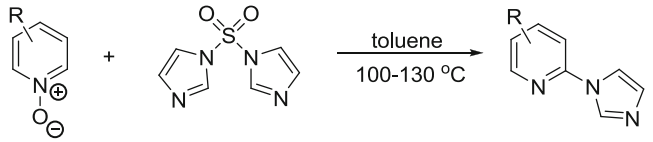
By using this methodology, a new and useful procedure for macrocyclization of linear peptides has been advanced. The side chains of natural amino acids, such as tyrosine, lysine, and histidine, were allowed to react intramolecularly with pendant carboxamide derivatives of pyridine *N*-oxides, which were selectively activated by the phosphonium salt, PyBroP (Scheme 18) [44]. The reaction proved to be mild, rapid, and efficient with a potentially large substrate scope. A great deal of examples can be demonstrated, including a novel aza-analogue of the ring system of vancomycin.

A number of aza-aromatic *N*-oxides, such as pyridine, quinoline, and pyrimidine *N*-oxides, were converted into the corresponding α-imidazolyl-substituted heteroarenes in good yields on treatment with sulfuryl diimidazole in nonpolar solvents at elevated temperatures (Scheme 19) [45].

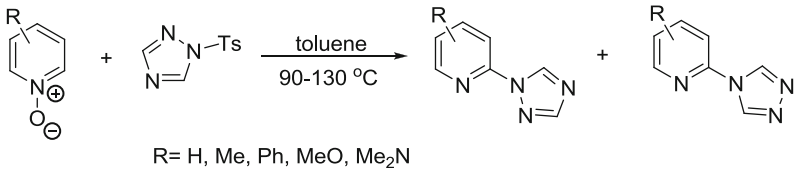
Heteroaromatic *N*-oxides were also converted into their α-triazolyl and α-diazolyl derivatives by reacting with the corresponding *para*-toluenesulfonylazoles and the Hunig's base at elevated temperature (Scheme 20) [46].



Scheme 18 Macrocyclization exploiting amination of pyridine *N*-oxides



Scheme 19 Introduction of the imidazole moiety into pyridines

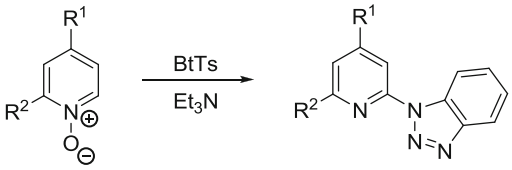


Scheme 20 Introduction of the triazole moiety into pyridines

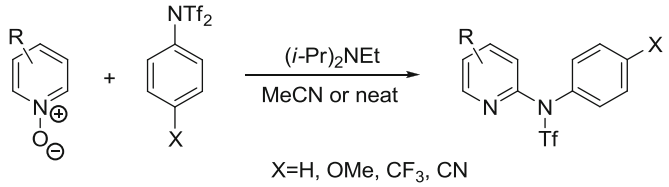
α-Benzotriazolyl-substituted pyridines, quinolines, and isoquinolines have been prepared through C–H functionalization of pyridine, quinoline, and isoquinoline *N*-oxides, as starting materials, with 1-tosylbenzotriazole in the presence of triethylamine (Scheme 21) [47]. Treatment of α-benzotriazolyl derivatives of pyridines, quinolines, and isoquinolines with hydrogen peroxide in glacial acetic acid afforded the corresponding azine *N*-oxides. The reaction of 1-(2-pyridinyl)-benzotriazole with alkyl halides or tosylates led to the corresponding *N*-alkylpyridinium salts.

A variety of pyridine, quinoline, isoquinoline, and pyrimidine *N*-oxides were converted into the corresponding α-*N*-aryltriflamido-substituted aza-aromatics in good yields on treatment with *N*-aryltriflimides, both neat and in solution, at a temperature ranging from ambient to 100 °C (Scheme 22) [48].

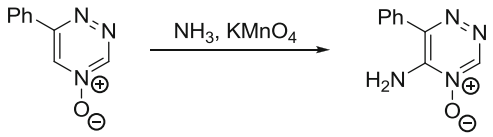
As for direct amination of electron-deficient heteroaromatic *N*-oxides, the combination of liquid ammonia and potassium permanganate is known to be a very effective system for such type of C–H functionalizations. It has been reported that 6-phenyl-1,2,4-triazine-4-oxide can easily be aminated in liquid ammonia on treatment with potassium permanganate to give 5-amino-6-phenyl-1,2,4-triazine 4-oxide (Scheme 23) [49].



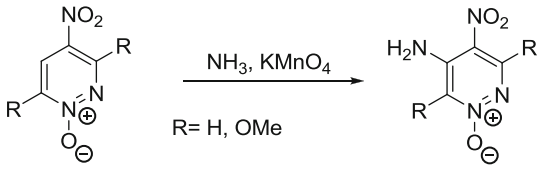
Scheme 21 Introduction of the benzotriazole fragment in the pyridine ring



Scheme 22 C–H functionalization of pyridine *N*-oxides with *N*-aryltriflimides



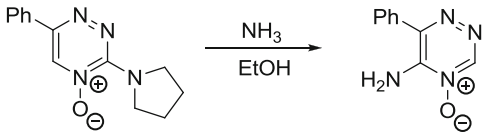
Scheme 23 Amination of triazine *N*-oxides in liquid $NH_3/KMnO_4$ system



Scheme 24 Amination of pyridazine *N*-oxides using $NH_3/KMnO_4$ system

The nitro group plays an important role in activation of diazine *N*-oxides for the amination reaction, and indeed, treatment of 4-nitropyridazine 1-oxide or 3,6-dimethoxy-4-nitropyridazine 1-oxide with potassium permanganate in liquid ammonia affords the corresponding 5-amino-4-nitropyridazine 1-oxides in reasonable to good yields (Scheme 24) [50].

Interestingly, the reaction of 3-pyrrolidino-1,2,4-triazine 4-oxide with ammonia has been established to give 5-amino-1,2,4-triazine 4-oxide, due to the *tele*-substitution process with elimination of pyrrolidine (Scheme 25) [51]. As for the mechanism of this amino-dehydrogenation reaction, a sigmatropic shift of hydrogen has been postulated, substantiated by registration of the key intermediates.



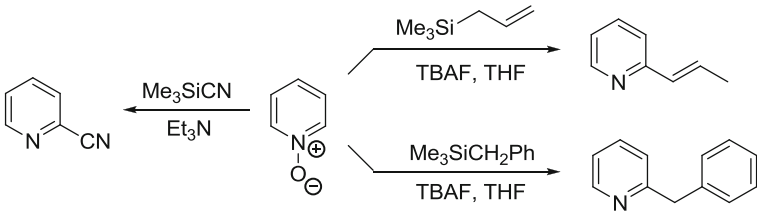
Scheme 25 *tele*-substitution of hydrogen observed in the reaction of 3-pyrrolidino-1,2,4-triazine 4-oxide with NH_3

The chemistry of C–H functionalizations in the series of 1,2,4-triazines and 1,2,4-triazine *N*-oxides has been discussed in the recently published review articles (1,2,4-Triazine *N*-oxide: [52, 53]).

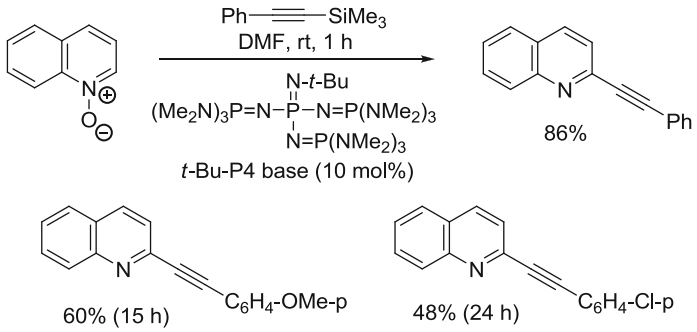
3 Metal-Free C–H Functionalization with Carbon Nucleophiles

The reaction of heteroaromatic *N*-oxides with organosilicon compounds is known as an important method for introduction of carbon functionalities in heteroaromatic rings (Scheme 26) [54–56]. Pyridine *N*-oxide has been established to react with an excess of trimethylsilyl cyanide and triethylamine in acetonitrile at 80 °C to give 2-cyanopyridine in a high yield. Other heterocyclic *N*-oxides, such as quinoline, isoquinoline, pyrimidine, pyrazine, and quinoxaline *N*-oxides, have also been converted on treatment with trimethylsilyl cyanide into the corresponding cyano compounds. It has also been found that pyridine *N*-oxide and other azine or benzazine (pyridine, quinoline, or isoquinoline) *N*-oxides react smoothly with an excess of allyltrimethylsilane or benzyltrimethylsilane in the presence of catalytic amounts of tetrabutylammonium fluoride (TBAF) trihydrate. When reacting with an excess of allyltrimethylsilane in THF under these conditions, pyridine *N*-oxide gave 2-propenylpyridine in a good yield, whereas the same starting material, pyridine *N*-oxide, was converted by action of benzyltrimethylsilane into 2-benzylpyridine in 70% yield.

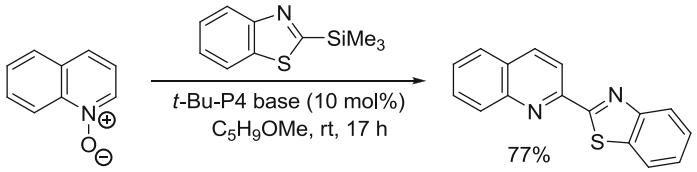
The C–H functionalization of quinoline *N*-oxide has recently been investigated by using alkynylsilanes and heteroarylsilanes in the presence of phosphazene P4 base as a catalyst [57–69], and this alkynylation reaction proceeding selectively at 2-position of the pyridine ring proved to occur successfully via nucleophilic addition-elimination process. As described above, organosilicon nucleophiles have been used to introduce cyano or benzyl moieties into aza-aromatics, and several examples for incorporation of alkynyl or aryl fragments by using alkynylsilanes or arylsilanes have recently been published. A new simple process has been developed for introducing carbon functionality via organocatalytic deprotonative addition of nucleophile in the presence of phosphazene base catalyst and organosilicon compounds. The addition-elimination reaction of quinoline *N*-oxide with trimethylsilyl phenylacetylene has been shown to proceed smoothly in DMF in the presence of



Scheme 26 C–H functionalization of pyridines with organosilicon compounds



Scheme 27 Alkynylation of quinoline *N*-oxide

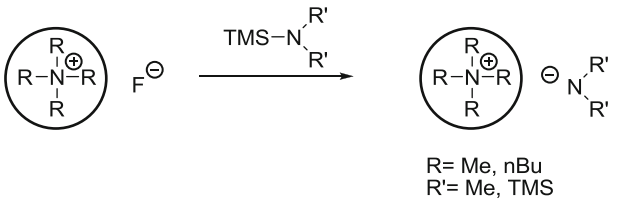


Scheme 28 Synthesis of 2-benzothiazolyl-substituted quinoline

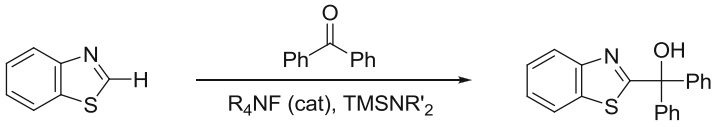
10 mol% P4-*t*-Bu to give 2-phenylethynyl-substituted quinoline in high yield (Scheme 27) [70]. As for other alkynylsilanes, trimethylsilyl-4-methoxyphenyl- and trimethylsilyl-4-chlorophenyl-substituted acetylenes have also been used, and the reaction with the latter alkynylsilane proved to proceed somewhat slower.

The reaction of quinoline *N*-oxide with 2-trimethylsilylbenzothiazole was also found to proceed smoothly under similar reaction conditions at room temperature. Use of cyclopentylmethyl ether as solvent gave the best results, and the desired heterobiaryl derivative was obtained in good yield (Scheme 28) [70].

Another approach for organocatalytic C–H functionalization of heteroaromatic *N*-oxides has been reported by using in situ generated ammonium amides and C-nucleophiles (Scheme 29), which are introduced into heteroaromatics through a sequence of the addition and elimination steps to give α-substituted azines under metal-free reaction conditions.



Scheme 29 Generation of ammonium amides



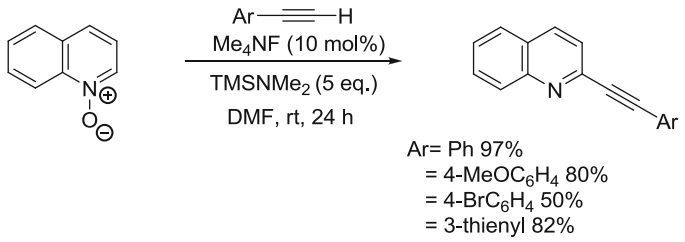
Scheme 30 C–H functionalization of benzothiazole catalyzed by in situ generated ammonium amide

It is worth noting that ammonium amides, generated in situ from a mixture of aminosilanes and ammonium fluorides, have recently been employed as bases for organocatalytic deprotonative C–H functionalization of heteroaromatics under mild conditions (Scheme 30) [71].

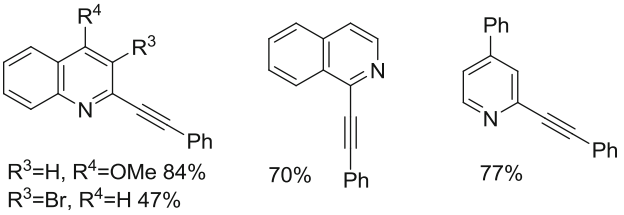
The organocatalytic transformation of azine *N*-oxides into the corresponding 2-substituted heteroaromatics by using in situ generated ammonium amides has first been reported. The catalytic addition-elimination reaction of quinoline *N*-oxide with phenylacetylene by using in situ generated ammonium amide derived from ammonium fluorides and dimethylaminotrimethylsilane has been investigated. When TBAF was allowed to react with quinoline *N*-oxide in the presence of 2.5 equiv. dimethylaminotrimethylsilane in toluene at room temperature, 2-phenylethynyl-substituted quinoline was obtained in 27% yield. The solvent was then switched to DMF, thus improving yield up to 49%. When TBAF was used in the presence of 5 equiv. dimethylaminotrimethylsilane in DMF, 89% yield of the product was reached. Use of tetramethylammonium fluoride (TMAF) instead of TBAF gave excellent results, and the same product was isolated in 97% yield (Scheme 31) [72]. The reactions of quinoline *N*-oxide with 4-methoxyphenyl-, 4-bromophenyl-, and thienyl-substituted acetylenes proved to proceed well to give the corresponding 2-substituted quinolines.

4-Methoxyquinoline *N*-oxide and 3-bromoquinoline *N*-oxide were reacted with phenylacetylene under the same reaction conditions to give the desired ethynylquinoline derivatives in 84% and 47% yields, respectively. The reaction of isoquinoline *N*-oxide with phenylacetylene gave 1-phenylethynylisoquinoline in 70% yield. The interaction of 4-phenylpyridine *N*-oxide with phenylacetylene also proceeded smoothly to give 2-phenylethynyl derivative in 77% yield (Scheme 32) [72].

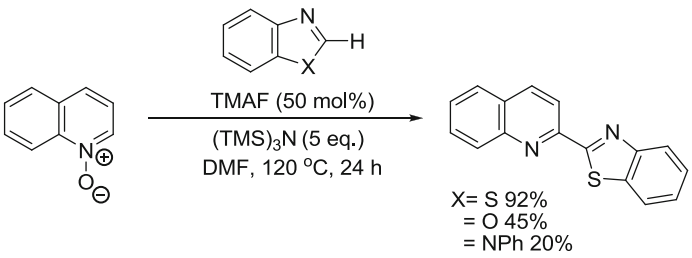
The reaction of quinoline *N*-oxide with benzothiazole was then investigated, and, being carried out under the same conditions, as in the case with phenylacetylene, it



Scheme 31 Alkynylation of quinoline *N*-oxide



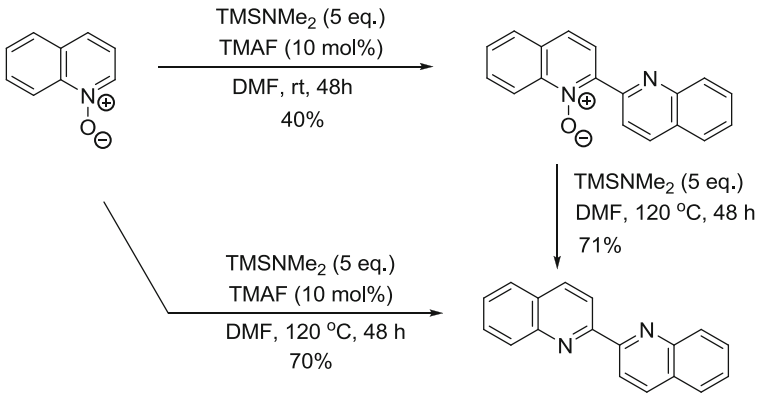
Scheme 32 Synthesis of alkynyl-substituted heteroaromatics



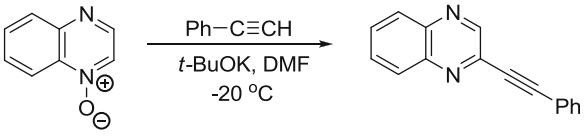
Scheme 33 Heterobiaryl synthesis using ammonium amide catalyst

proved to be sluggish. The reaction temperature was elevated to 120 °C, thus affording 2-benzothiazolylquinoline in 18% yield. When *tris*-trimethylsilylamine was used instead of dimethylaminotrimethylsilane, the same product was obtained in 39% yield. When amount of TMAF was enhanced to 30 mol%, yield was improved to 65%, while use of 50 mol% of TMAF enabled to obtain the product in 92% yield. Similarly, the reactions of quinoline *N*-oxide with benzoxazole and 1-phenylbenzimidazole were carried out to give 2-heteroarylated quinolines (Scheme 33) [72].

In the reaction of quinoline *N*-oxide with 1-phenylbenzimidazole, 2,2′-biquinoline derivative was isolated as a side product. In order to examine the reaction pathway, quinoline *N*-oxide was allowed to react without 1-phenylbenzimidazole. Quinoline *N*-oxide was treated with TMAF and dimethylaminosilane at room temperature, and 2,2-biquinoline *N*-oxide was obtained in 40% yield. On the other hand, the same reaction at 120 °C gave deoxygenated 2,2-biquinoline, which was obtained in 70%



Scheme 34 Biquinoline formation in the presence of ammonium amide catalyst



Scheme 35 Alkynylation of quinoxaline *N*-oxide

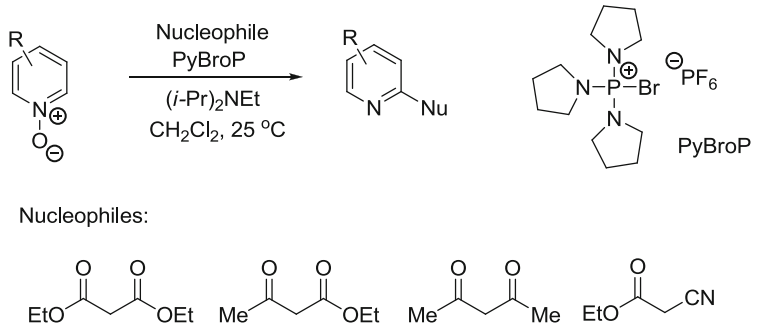
yield. In order to clarify the difference, 2,2-biquinoline *N*-oxide was treated with dimethylaminosilane at 120 °C, and the deoxygenated 2,2-biquinoline was isolated (Scheme 34) [72].

As for alkynylation of heteroaromatic *N*-oxides, it has been reported that azine *N*-oxides react with lithium and/or potassium acetylenides to give the corresponding ethynylazines. It is worth noting that the reaction with lithium acetylenide requires a subsequent acylation of the intermediate anionic adduct for rearomatization, whereas in case of potassium acetylenide, the *auto*-aromatization takes place (Scheme 35) [73].

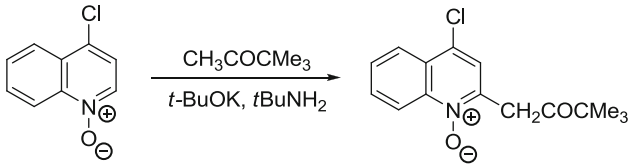
Carbon nucleophiles are able to react with heteroaromatic *N*-oxides, and these addition-elimination transformations have been found to proceed effectively in the presence of the phosphonium salt PyBroP (Scheme 36) [74]. A series of carbonyl compounds capable of enolization have been involved in the reaction with pyridine *N*-oxides to give 2-substituted pyridines in moderate yields, and in all these cases, it proved necessary to use threefold excess of nucleophile relative to the *N*-oxide in order to avoid further addition of the reaction product to the starting azine *N*-oxide.

A good example of the oxidative C–H carbon functionalization of heteroaromatic *N*-oxide is the reaction of 4-chloroquinoline 1-oxide with pinacolone and *t*-BuOK in *t*-$BuNH_2$ at −10 to −15 °C, which results in the formation of 4-chloro-2-pinacolylquinoline 1-oxide in good yield (Scheme 37) [75].

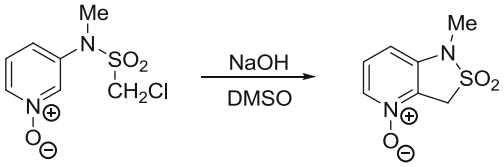
Another approach exploits vicarious nucleophilic substitution (VNS) [76]. Indeed, efficient syntheses of isothiazolo[4,3-*b*]pyridines and isothiazolo[4,3-*b*]-quinolines have been advanced via intramolecular VNS of hydrogen in pyridine and quinoline



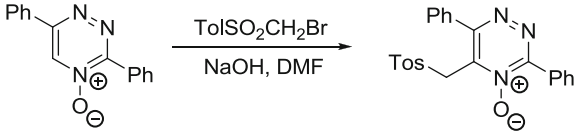
Scheme 36 Introduction of carbon functionalities into pyridine *N*-oxides



Scheme 37 Introduction of carbon functionalities into quinoline *N*-oxides



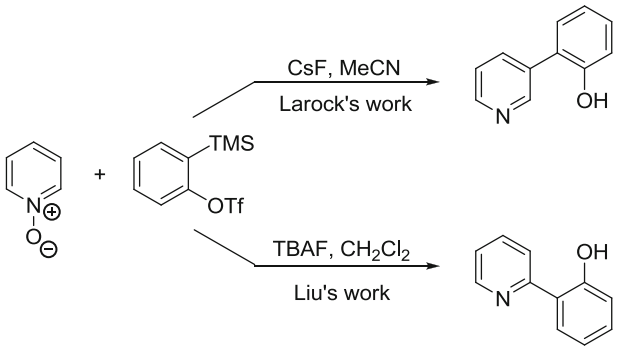
Scheme 38 Intramolecular vicarious nucleophilic substitution of hydrogen



Scheme 39 Vicarious nucleophilic substitution in triazine *N*-oxides

N-oxides bearing the fragment of chloromethanesulfonamide. These derivatives can be obtained from 3-aminopyridine and 3-aminoquinoline (Scheme 38) [77].

It has been reported that 3,6-diaryl-1,2,4-trizine-4-oxides undergo nucleophilic substitution of hydrogen with the α-halomethyl aryl sulfones by two alternative pathways, namely, by means of VNS or through intramolecular deoxygenative process. The first pathway has been found to be dominative one in the reaction of 1,2,4-triazine-4-oxides with bromomethyl tolyl sulfone to yield 5-tosylmethyl-1,2,4-triazine 4-oxides (Scheme 39), while the reaction of the same triazine



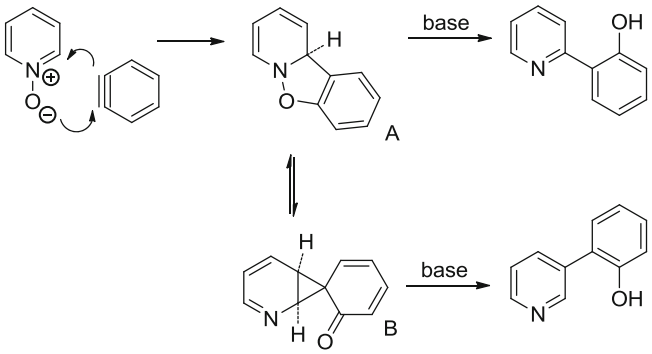
Scheme 40 Reaction of pyridine *N*-oxide with benzyne

4-oxide with chloromethyl aryl sulfones leads to 5-arylsulfonylchloromethyl-1,2,4-triazines [78].

4 Functionalization with Arynes

Abramovich and Shinkai have reported that pyridine *N*-oxides react with benzyne to give a mixture of 2- and 3-(2-hydroxyphenyl)pyridines in low yields [79]. As 2-phenylpyridine derivatives appear to be important ligands for green phosphor emitters, such as $Ir(ppy)_3$, for instance, a selective synthesis of 2-aryl-substituted pyridines from readily available benzyne precursor is desired to be achieved. Larock has developed a regioselective synthesis of 3-(2-hydroxyphenyl)-substituted pyridine, using CsF in acetonitrile [80]. It has been suggested that an excess of basic pyridine *N*-oxide or cesium fluoride over benzyne is crucial for the formation of 2-substituted regioisomer. Liu altered Larock's conditions by steadily increasing proportions of CsF and *N*-oxide in acetonitrile, whereas amount of benzyne was kept at the level of 1.0 equiv. (Scheme 40) [81]. It has been revealed that increasing proportions of pyridine *N*-oxide and CsF significantly enhance the formation of 2-substituted regioisomer. Also it has been observed that an excess of pyridine *N*-oxide (or TBAF) enhances yields of 2-substituted regioisomer. Among these parameters, use of a less polar solvent, like dichloromethane, appears to be the best choice, so that 1.5 equimolar quantities of pyridine *N*-oxide and TBAF are enough to alter the regioselectivity in favor of 2-substituted regioisomer.

Under the Larock's reaction conditions, where bases like pyridine *N*-oxide and cesium fluoride are in deficient proportions, transformation of the intermediate A into 2-(2-hydroxyphenyl)pyridine is unlikely to occur, because base concentration is not sufficient to intercept species A through deprotonation. Therefore, the formation of 3-regioisomer seems to proceed through rearrangement of the intermediate B into 3-(2-hydroxyphenyl)pyridine via loss of the cyclopropyl CH proton that is more acidic than C–H proton in the intermediate A. An excess of pyridine *N*-oxide and



Scheme 41 A plausible mechanism for the reaction of pyridine *N*-oxide with benzyne

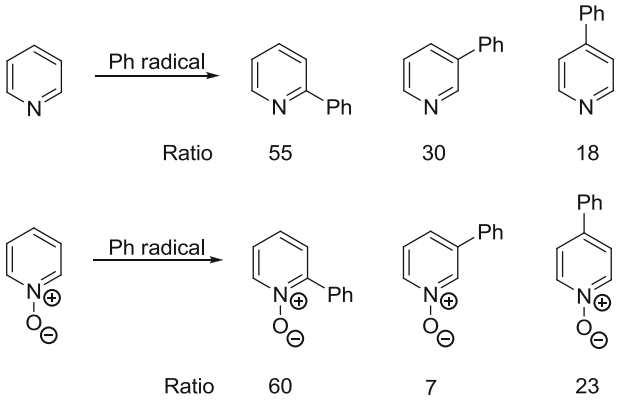
cesium fluoride (1.5 equiv.) in dichloromethane enables interception of the initially formed intermediate A to give 2-substituted pyridine predominantly (Scheme 41).

Since the aryne chemistry [82–84] is a very important synthetic tool for transformation of heteroaromatic *N*-oxides, the further studies expanding application of this methodology are expected to be done.

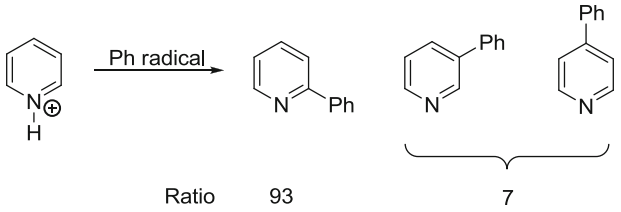
5 C–H Functionalization Using Radical Reactions

Additions of radical species to aromatic systems have always been an important research subject from the earliest days of organic chemistry. Also it is known that since 1890s chemists had been investigating reactions involving the addition of aryl radicals to heteroaromatic systems, such as pyridine [85, 86]. A considerable progress in development of this methodology, as a synthetically useful transformation, has been achieved during the twentieth century [87–89]. At the beginning of these studies the efficiency of radical reactions in the series of pyridines remained low, since they produced a lot of regioisomeric products; however, in the 1960s, it became clear how to control the regioselectivity of the radical addition reactions. The addition of phenyl radicals to pyridine *N*-oxide proved to occur in rather good yield, showing an enhanced regioselectivity for the position 2 of the pyridine ring, in comparison with a similar reaction of pyridine (Scheme 42) [90].

Later, professor Minisci made a great contribution to this field demonstrating a benefit of acidic conditions, which enabled chemists to improve both reaction rates and positional selectivity for radical additions to heteroaromatic bases (Scheme 43) [91]. Minisci and other organic chemists refined the radical reactions to the point where they constitute the effective set of distinct transformations. This is why the radical additions to heteroaromatic bases are sometimes referred in the literature as the "Minisci reactions." Indeed, the Minisci reactions represent a powerful tool for the C–H functionalization of heteroaromatic compounds [92]. The reactions are



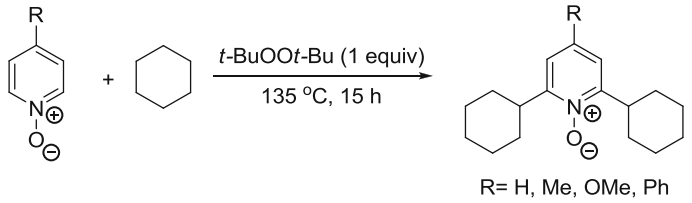
Scheme 42 Reactions of pyridine and pyridine *N*-oxide with phenyl radical



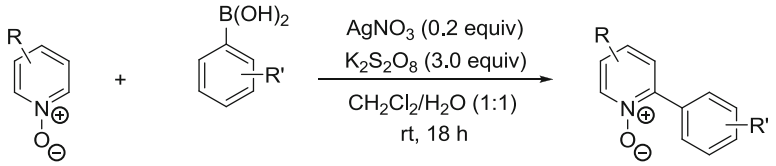
Scheme 43 Reactions of NH-pyridinium salt with phenyl radical

considered as complementary to other C–H functionalizations, such as carbocation- or carbanion-mediated reactions.

Radical reactions have recently got a wide attention of many researchers as a very important methodology for green or sustainable chemistry [93–97]. As for the C–H functionalization of heteroaromatic *N*-oxides, the metal-free cross-coupling reactions of aza-aromatics with alkanes have been reported by using radical species. In the presence of *t*-Bu-OO*t*-Bu, pyridine *N*-oxide derivatives were found to react with alkanes to give the corresponding alkyl derivatives of nitrogen heterocycles in good yields (Scheme 44) [98]. This reaction is considered to be very important and indicative, as one of the oxidative cross-couplings with functionalization of two different C–H bonds. Moreover, in view of the current strict guidelines, limiting the level of transition metals in pharmaceuticals, the C–C bond forming reactions, proceeding without transition metals, are worth noting as a remarkable synthetic approach. The nitrogen-atom activation appears to be a key step to achieve the desired coupling, and it has been found that pyridine *N*-oxides are superior substrates for the radical-based arene-alkane cross-coupling. For example, the reaction of pyridine *N*-oxide with an excess of cyclohexane proceeds smoothly in the presence of *t*-BuOO*t*-Bu at 135 °C for 15 h, thus affording 2,6-dialkylated product in 40% yield, whereas only traces of the same product can be obtained when pyridine reacts with cyclohexane under similar reaction conditions and no changes



Scheme 44 Reactions of pyridine *N*-oxides with cyclohexyl radical



Scheme 45 Radical reaction of pyridine *N*-oxides with arylboronic acid

are observed on increasing amount of peroxide. It has clearly been shown that the *N*-oxide moiety enhances both the reactivity and regioselectivity.

The efficient alkylation of pyridine *N*-oxide is still a rare approach in comparison to the emerging arylation or alkenylation methods using transition metal catalysts, which have already been mentioned in the introduction. A variety of electronically and structurally diverse pyridine *N*-oxides have been shown to react with cyclohexane in the presence of *t*-BuOO*t*-Bu to give the corresponding alkylated products in good yields. These couplings of pyridine *N*-oxides take place with various electron-donating and electron-withdrawing substituents in the pyridine ring, not much affecting their efficiency. When a substituent is present in 4-position of the pyridine ring, 2,6-dialkylation products are formed predominantly, while with a substituent at 2-position, the monoalkylation becomes the major pattern of the reaction. Pyridine *N*-oxides of their aza-aromatic analogues, such as quinoline *N*-oxide derivatives, also react smoothly with cyclohexane. It is worth noting that the reaction always takes place on the oxygenated *N*-heteroaromatic ring, leaving other aromatic rings to be intact. Similarly to cyclohexane, cyclooctane and cycloheptane react smoothly with pyridine *N*-oxide. Also the reaction takes place with norbornene and 1,4-dioxane, thus giving rise to structurally interesting molecules.

A new approach for direct arylation of pyridine *N*-oxides with arylboronic acids through C–H functionalization has been developed (Scheme 45) [99]. This reaction can be performed at room temperature using catalytic silver (I) nitrate in the presence of potassium persulfate, thus giving 2-aryl derivatives of pyridine *N*-oxides.

The C–H functionalization of heteroaromatic compounds using radical reactions is considered to be a rapidly growing area, and new findings on radical C–H transformations can be applied to modify the structure of heteroaromatic *N*-oxides [100, 101].

6 Conclusion

Various metal-free reactions have been described in this chapter, and many of them are found to be effective for C–H functionalization of heteroaromatic *N*-oxide. Both heteroatom and carbon functionalities can be introduced successfully at the α-position of nitrogen heteroaromatic compounds. Significant progress has been made during the last 10 years, and this area is considered to be still expanding rapidly due to a strong demand of green chemistry or environmentally benign synthesis. Heteroaromatic *N*-oxides are important compounds, especially for material and medicinal chemistry, and there is no doubt that the development of new metal-free processes will contribute to this area, providing a facile access to well-designed functional molecules for material science and drug discovery research. Further progress and development are expected to be made, while metal-free functionalizations of C–H bonds in aromatic and heteroaromatic compounds appear to be more and more attractive for researchers in both academic and industrial spheres.

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The S_N^H-Amination of Heteroaromatic Compounds

Anna V. Gulevskaya and Alexander F. Pozharskii

Abstract The review surveys the data on amination of electron-deficient aromatic heterocycles by using the methodology of nucleophilic substitution of hydrogen (S_N^H). The recent advances in this area involve many new aspects of the S_N^H-amination, including a wide range of heteroaromatic substrates and new types of aminating reagents, metal-free catalysts, solvents, and the hydride ion acceptors. The review demonstrates that the S_N^H approach is becoming an increasingly popular and important synthetic alternative to the classical and transition metal-catalyzed amino-dehalogenation reactions.

Keywords Amination · Heterocycles · Nucleophilic aromatic substitution of hydrogen

Contents

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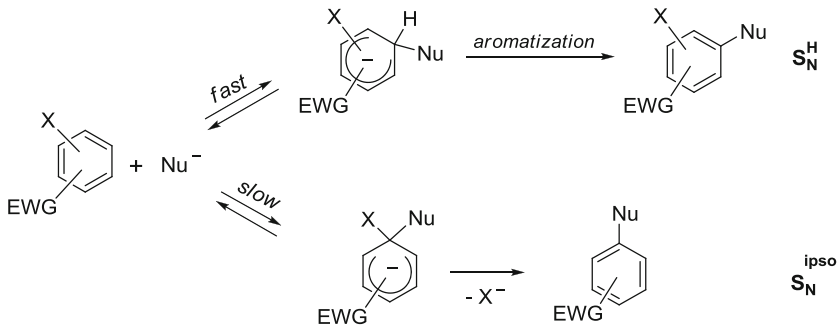
1 Introduction

Aromatic and heteroaromatic amines are essential subunits of a wide variety of biologically active compounds of both natural and synthetic origin [1, 2] with their numerous applications in organic, inorganic, organometallic, and material chemistry [3]. Therefore, development of convenient, simple, and efficient synthetic protocols for incorporation of amino-, alkylamino-, or arylamino groups into aromatic and heteroaromatic rings is of great importance.

A classical strategy for the synthesis of amino(het)arenes involves nucleophilic displacement of a good leaving group (the so-called *ipso*-substitution) in an aromatic substrate, which has usually to be activated by electron-withdrawing substituents or ring heteroatoms [4]. Transition metal-catalyzed amination of halo (het)arenes is a more versatile and general method since there is no need to activate the substrate in this case [5]. The most characteristic and impressive example of such type of reactions is the Buchwald–Hartwig amination [6]. However, a common drawback of all methods based on *ipso*-substitution is the requirement that a halogen atom or pseudo halogen nucleofuge has to be present in an aromatic substrate. In addition, these protocols can scarcely be performed at room temperature and often require expensive catalysts and ligands.

Direct nucleophilic substitution of hydrogen (S_N^H) for amino functionality seems to be a very attractive alternative to the abovementioned methods. The problem, however, is that in these amino-dehydrogenation reactions the hydride ion, which is a very poor leaving group, should formally be replaced. It was the outstanding Russian chemist Alexei Chichibabin who had first suggested the ways to solve this problem. On the example of azines, he had shown that a heteroaromatic substrate in such direct amination reactions had to be activated, at least by one aza group, and a nucleophilic reagent should be strong enough (e.g., $NaNH_2$, anhydrous powdered KOH) [7]. Then other researchers have found that a similar effect or even a higher activation can be achieved in the series of azoles, quinones, nitroarenes, azine N-oxides, and other electron-deficient aromatics.



EWG - electron-withdrawing group (NO_2, aza group, M^{n+} *etc.*)
X - good leaving group (Hal, NO_2 etc.)

Scheme 1 Addition-elimination mechanisms of nucleophilic aromatic substitution

A detailed study of the nucleophilic aromatic substitution of hydrogen has been initiated at the Urals State Technical University (Russia) in the 1970s. In the first review on this topic, it was suggested to use the symbol S_N^H in order to distinguish these reactions from the classical nucleophilic *ipso*-substitution S_N^{ipso} Ar [8]. Later, a number of special reviews [9–38] and also the book *Nucleophilic Aromatic Substitution of Hydrogen* [39], which accumulated a considerable body of data on conditions, kinetics, structure of intermediates, electrochemical and mathematic modeling, as well as plausible mechanisms and the general concept of the S_N^H-reactions, have also been published.

Gradually, the S_N^H-methodology has gained attention of chemists as a powerful synthetic tool. Modern S_N^H-procedures allow to introduce into electrophilic aromatics not only amino groups but also residues of O-, C-, S-, Hal-, and P-nucleophiles, and these processes often take place at ambient or even at low temperatures. Not surprisingly, this area is actively developed and a very promising field of chemistry.

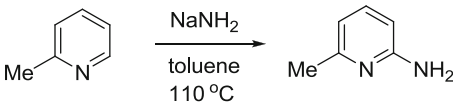
According to the accepted concept, reactions of electrophilic (het)arenes with nucleophiles usually proceed via the two-step "addition-elimination" mechanism (Scheme 1) (for a tutorial review, see [36]). At the first step, the formation of two types of intermediates, the σ^X- and σ^H-adducts, is considered to occur. As a rule, nucleophilic addition to unsubstituted ring carbon atom prevails over the *ipso*-attack. Even in those cases, where a good leaving group X is present in an aromatic ring, a rapid and reversible formation of the σ^H-adducts, as kinetically controlled species, appears to be a primary process, proceeding faster than *ipso*-substitution. In other words, from the mechanistic point of view nucleophilic *ipso*-substitution is a secondary process. σ^H-Complexes are usually more stable than their σ^X-counterparts, and the process of their aromatization via elimination of the hydride ion is a more difficult one. As a result, the initially formed σ^H-adducts are slowly transformed into the σ^X-complexes, which irreversibly loose the X^- anions, thus giving rise to products of the classic S_N^{ipso}-reactions.

Fortunately, along with direct elimination of the hydride ion, which demands rather drastic reaction conditions, aromatization of the σ^H-complexes can be realized through other reaction pathways, such as oxidative nucleophilic substitution of hydrogen or elimination of an auxiliary leaving group, located in vicinal or distant positions to the addition site or even at the nucleophilic center of a nucleophilic reagent (*cine*-, *tele*- and vicarious nucleophilic substitution (VNS), respectively). The S_N^H amination reactions can also proceed via even more complicated mechanisms, including the sequence of ring opening and ring closure steps, or participation of catalysts.

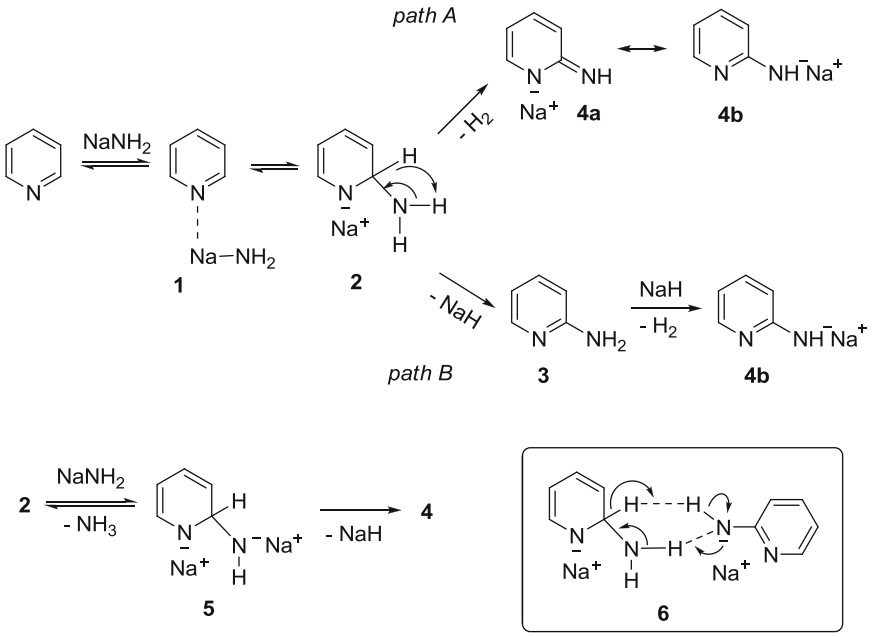
The present review surveys the data on the S_N^H-amination reactions of heteroaromatic substrates published mainly during the last decade. The S_N^H data accumulated in the literature are distributed into five sections, in accordance with the accepted mechanisms, operating in these S_N^H-amination reactions. A short historical background, reactivity, scope, and limitations for the S_N^H-amination of heteroaromatic substrates and selectivity of the reactions, as well as examples of synthetic procedures, are presented in the chapter.

2 The Classical Chichibabin Amination

The direct amination of azines with sodium amide was first discovered by Chichibabin and Zeide in 1914, when they observed unexpectedly the formation of 2-amino-6-methylpyridine, while attempting to metallate the methyl group in 2-picoline (Scheme 2) [7]. In subsequent years, Chichibabin together with his student associates have succeeded to extend this method for amination of pyridine, quinoline, isoquinoline, and their numerous derivatives. Pyridine was shown to react with $NaNH_2$ (toluene, 110°C) to give 2-aminopyridine (75%) as the major product together with a small amount of 4-aminopyridine. At a higher reaction temperature (180°C) 2,6-diaminopyridine was obtained in good yield and a small amount of 2,4,6-triaminopyridine. Nowadays the Chichibabin amination reaction is well recognized as an outstanding methodology for the direct amino-dehydrogenation of electron-deficient aromatics. This method proved to have a strong influence on the development of heterocyclic chemistry. In particular, its value in pyridine chemistry can hardly be overestimated. Indeed, the Chichibabin reaction is of great industrial importance since many aminopyridines are valuable intermediates, especially in the synthesis of pharmaceuticals. Application of this amination methodology to condensed imidazoles (benzimidazoles, naphthoimidazoles, etc.) and perimidines proved also to be extremely fruitful [9, 10]. However, a serious drawback of the classical Chichibabin reaction is a poor tolerance of many functional groups to so aggressive and basic reagent as $NaNH_2$ under elevated temperatures. Three comprehensive reviews on the Chichibabin reaction can be recommended [9, 10, 15] and the following short survey outlines these data.



Scheme 2 The Chichibabin amination of 2-picoline



Scheme 3 Mechanisms suggested for the Chichibabin reaction

The classical Chichibabin reaction is normally to be carried out on heating (>100°C) in a media, which is inert towards sodium amide (aromatic hydrocarbons, *N*,*N*-dialkylanilines, a mineral oil), or without any solvent at all. The amination under these heterogeneous conditions is supposed to proceed on the surface of sodium amide particles, which are insoluble in all abovementioned solvents. Vigorous hydrogen gas evolution and intense red color are typical indicators of the reaction progress.

The mechanism of the Chichibabin reaction is still not clear, mainly due to the difficulties to handle with highly reactive alkali amides and also to study reaction kinetics under such specific conditions. Nevertheless, several remarkable observations shed some light on the mechanistic features of the process. Indeed, it has been found that heterocycles with pK_a values of 5–6 are aminated easily, while aromatic substrates with a lower basicity exhibit a low reactivity or undergo decomposition. Dependence of the reaction on basic character of starting azaaromatics suggests that the formation of an adsorbtion complex of the type **1** (Scheme 3) with a weak coordination bond between the ring nitrogen atom and sodium ion may be

important. Such coordination might increase a positive charge on the ring α-carbon atom, thus facilitating nucleophilic addition of the amide ion. Anyway, anionic σ^H-complexes like **2** are commonly considered as the key intermediates. Moreover, they have been registered repeatedly by NMR in liquid ammonia solution, and several mechanisms for their aromatization have been suggested. The first one is elimination of hydrogen from the adduct **2** as shown in Scheme 3 (*path A*). The second one (*path B*) is envisaged as the preliminary elimination of sodium hydride, followed by deprotonation of aminopyridine **3**, thus producing hydrogen gas and sodium salt of 2-aminopyridine **4b**.

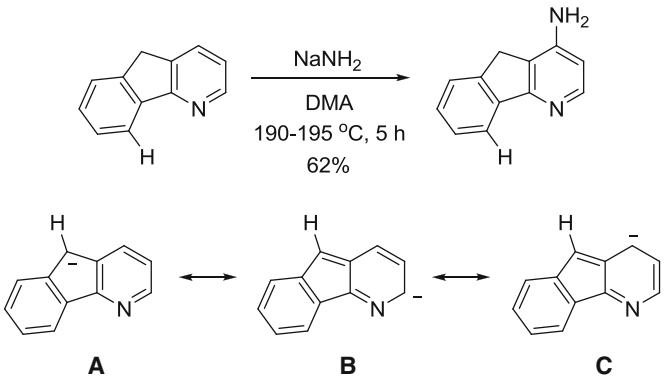
One more mechanism has been advanced, based on the fact that evolution of a considerable amount of ammonia gas takes place during the Chichibabin amination. Notably, this process becomes perceptible after some inductive period. Apparently, after accumulation of a certain amount of the adduct **2**, the latter can be converted into the dianion **5** by the action of sodium amide, thus producing ammonia. Obviously, elimination of the hydride ion from **5** should be strongly facilitated. It has been suggested that aromatization proceeds inside the intermediate bimolecular complex **6**, with participation of the salt **4** and σ-complex **5**. Therefore, the whole process appears to be autocatalytic one.

Some researchers have suggested that one-electron transfer from the amide ion to an aromatic substrate plays the key role in this reaction [9, 10, 40]. Dimerization of the starting aromatic compounds or the formation of partially hydrogenated dimers, which are sometimes observed in the course of the Chichibabin reaction, can be considered as indirect arguments in favor of this hypothesis.

The question of the rate-determining step in the Chichibabin reaction is still open. Clearly, it is difficult to expect that such a complex process can be controlled by any single parameter. On the basis of the rate of hydrogen gas evolution, the following sequence of the reactivity of aza-heterocyclic compounds has been established: 1-R-benzimidazoles > isoquinoline > 1-R-perimidines > benzo[*f*]quinoline > pyridine >> acridine. Evidently, this raw indicates that sodamide amination depends on number of factors, involving electron deficiency of the substrate C(α)-atom, ease of the σ^H-adduct aromatization, substrate basicity, etc. Evidently, acridine's position in this raw reflects the difficulty of the γ-amination.

The mechanism of the Chichibabin amination of pyridine by the action of sodium amide has recently been investigated theoretically by using the B3LYP/6-31+G(d) level of theory [41]. This work did not change the existing concepts. Once again, it has been shown that the reaction proceeds through the loss of hydrogen gas rather than it involves the formation of sodium hydride.

During the last decade, some additional efforts have been undertaken to improve the amination procedure [42]. A rare example of exclusive γ-amination of the pyridine ring has been found. 4-Azafluorene has been shown to undergo amination by the action of sodium amide in *N*,*N*-dimethylaniline to produce 1-amino-4-azafluorene in 62% yield (Scheme 4) [43]. The authors believe that the reaction proceeds via the initial formation of 4-azafluorenyl anion (**A**), in which the negative charge is localized mainly in α-position of the pyridine ring (see the resonance structure **B**), thus making C-1 to be less deactivated for a nucleophilic attack. Such



Scheme 4 The Chichibabin amination of 4-azafluorene

regioselectivity can also be explained by steric hindrances for the coordination of sodium amide with the ring nitrogen atom.

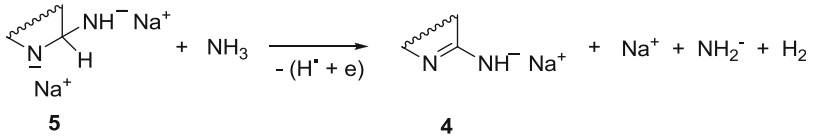
3 Oxidative Amination

3.1 Introduction of the NH_2 group

Oxidative amination of nitrogen heterocycles was first reported by Bergstrøm in the beginning of 1930, who studied the possibility of replacing nonpolar solvents used in the Chichibabin reaction by liquid ammonia – the only solvent, in which $NaNH_2$ and KNH_2 were dissolved [44]. Bergstrøm assumed that ammonia as NH-acid would accept the hydride ion from the dianionic σ^H-adduct **5**. Surprisingly, even at that time, aromatization of the intermediate σ^H-adduct was considered to be a stepwise process, involving a transfer of electron and a hydrogen atom to NH_3 molecule (Scheme 5) [45]. Notably, Bergstrøm, and later Zoltewich [46] and van der Plas [47], failed to aminate pyridine in liquid ammonia, even using a prolong time on heating in a sealed tube. This is why Bergstrøm used a more reactive quinoline as azaaromatic substrate for his further studies.

A more important Bergstrøm's idea was to use an oxidant (a "reducible substance," as he called it) to promote elimination of the hydride ion [45]. A number of compounds were tested for this purpose, namely $LiNO_3$, $NaNO_3$, $Sr(NO_3)_2$, $Ba(NO_3)_2$, KSCN, $Ba(SCN)_2$, NaN_3, and KIO_3. The best results were achieved with KNO_3. For instance, amination of quinoline in the presence of KNO_3 afforded 2-aminoquinoline in 22–53% yield, while without this oxidant it fell down to 6%.

For the first time this new method allowed alkylamination of pyridine and quinoline to be done into position 2 in 26–77% yields [48]. The reaction was carried out with an excess of alkylamine ($MeNH_2$, $BuNH_2$, *cyclo*-$C_6H_{11}NH_2$) in



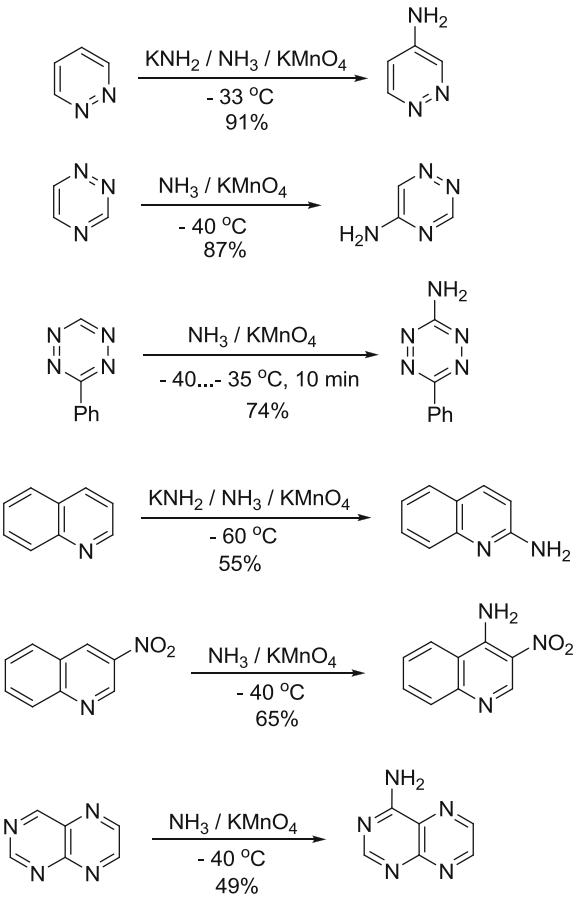
Scheme 5 Stepwise aromatization of the σ^H-adduct proposed by Bergstrøm

the presence of $KNH_2/NaNH_2$ eutectic and KNO_3. There are little doubts that under these conditions the corresponding alkylamides were initially formed, acting then as real nucleophiles. Serious drawbacks of this method were rather drastic reaction conditions, use of a sealed tube, a long reaction time, and inconvenience for process tracking. It was also discouraging that quite often in the presence of KNO_3 yields of alkylamination products were nearly the same because of a poor solubility of KNO_3 in alkylamines.

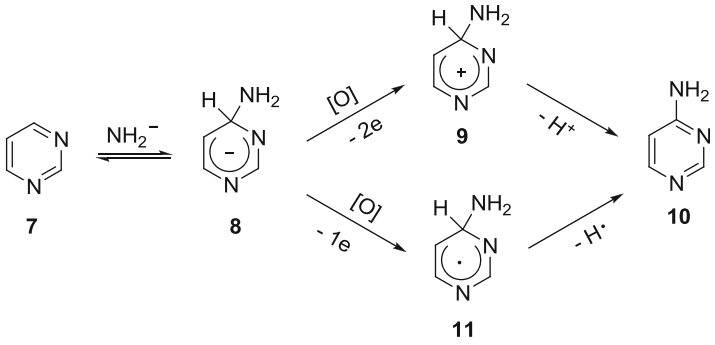
A major breakthrough in this field was achieved by Henk van der Plas with coworkers in early 1980s [12, 13, 49], when he had performed successfully a new version of the Chichibabin amination for the series of π-deficient azines in KNH_2/liq. NH_3 system, by using $KMnO_4$ as oxidant (Scheme 6). The reaction was carried out at a low temperature (in the range from −33 to −60°C) under homogeneous conditions, since $KMnO_4$ is well soluble in liquid ammonia. It is worth noting that, unlike the classical Chichibabin amination, new synthetic protocol did not show any dependence on the substrate basicity, demonstrating excellent yields of the amination products. Several excellent reviews on this topic have been published [12, 13, 16, 27, 28, 30, 39]. The mechanism of the reaction, the relative reactivity of azines, the site selectivity as well as effects of aza groups, substituents and benzene ring annelation have been thoroughly discussed. The following short survey outlines these data.

The formation of anionic σ^H-complexes of the type **8** (Scheme 7) in liquid ammonia has been proved by ^1H and ^{13}C NMR spectroscopy for many azine substrates [16, 30, 39]. Their further oxidation into heteroaromatic amines **10** is supposed to proceed via transfer of two electrons and proton or one electron and hydrogen atom, with the cationic **9** or radical **11** species as intermediates, correspondingly.

In the series of azaaromatics pyridine appears to possess the least electron deficiency and cannot be aminated under these conditions. In contrast, diazines, triazines, tetrazines, quinolines, quinoxalines, quinazolines, naphthiridines, polyazaaromatic compounds, and their nitro derivatives are able to undergo oxidative amination. Moreover, amination of highly π-deficient triazines, tetrazines, 3-nitropyridine, 3-nitroquinoline, etc. is possible to perform without KNH_2, since ammonia itself serves as nucleophile in such cases (Scheme 6). However, the more electron deficiency of an azine substrate, the less regioselectivity of the reaction. Oxidative amination of 3-nitropyridine in liquid ammonia with potassium permanganate affords a mixture of 2-amino-3-nitro- (33%), 4-amino-3-nitro- (24%), and

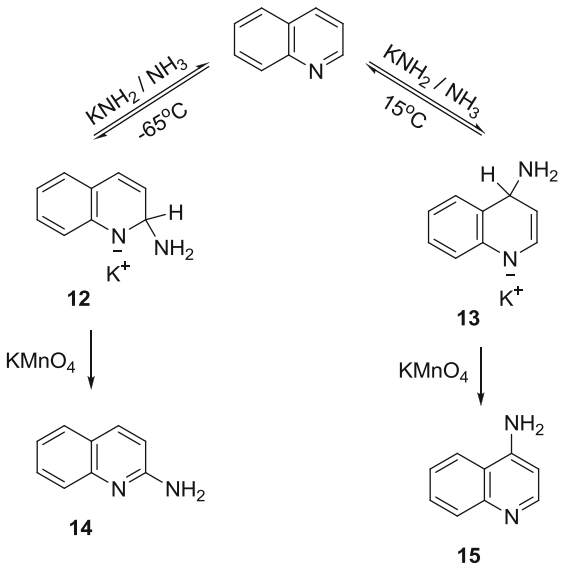


Scheme 6 Selected examples of oxidative amination reaction



Scheme 7 Proposed mechanisms for oxidative amination reaction

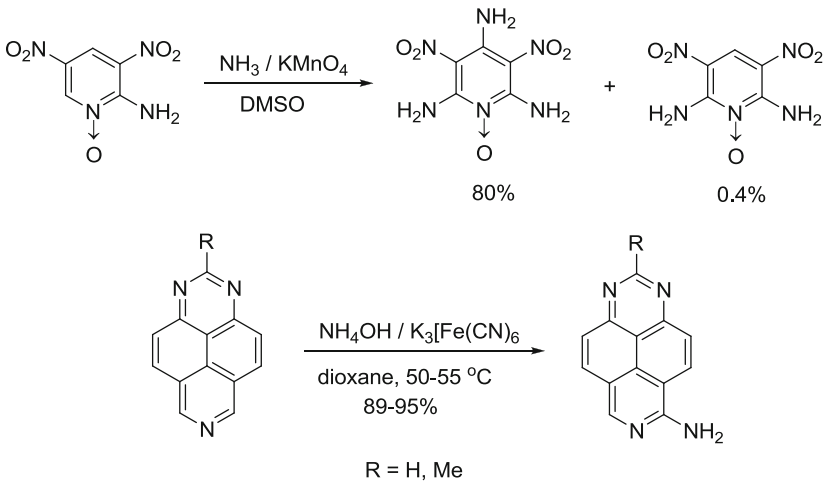
Scheme 8 Kinetic and thermodynamic control in oxidative amination of quinoline



6-amino-3-nitropyridines (19%) [50]. 3,5-Dinitropyridine undergoes plural amination giving a mixture of mono-, di-, and triamino derivatives [19].

Use of the liq. $NH_3/KMnO_4$ system at low temperatures has a great advantage, since it allows to leave untouched such functionalities in aromatics, such as halogens and alkoxy or alkylthio groups. For instance, dissolution of 2-chloro-3-nitropyridine in liquid ammonia containing potassium permanganate results in oxidative substitution of hydrogen giving 6-amino-2-chloro-3-nitropyridine [50].

It was found that the site of oxidative amination strongly depends on temperature [16, 30, 39]. This is illustrated by the following example [51, 52]. When quinoline is added to a solution of KNH_2 in liquid ammonia at −65°C, the 2-aminodihydroquinolinide **12** is formed (Scheme 8). Addition of $KMnO_4$ to this solution gives 2-aminoquinoline in 50–55% yields. However, when a solution of quinoline and KNH_2 in liq. NH_3 is warmed to about +15°C in a sealed tube, the 4-aminodihydroquinolinide **13** is nearly exclusively present. Addition of $KMnO_4$ to this solution gives 4-aminoquinoline in 60–65% yields. At intermediate temperatures, mixtures of **12** and **13** are registered by NMR spectroscopy. Evidently, formed at very low temperature adduct **12** is the kinetically favored product, while adduct **13** is the thermodynamically preferred. C(4)-Amino adduct **13** is more stable than C(2)-amino isomer **12** due to the aza-allylic resonance stabilization. It should be noted that besides temperature the final composition of the oxidative amination products depends also on the rates of the aromatization for isomeric σ^H-adducts. Indeed, quinoline, when dissolved in a solution of KNH_2 in liquid ammonia at −40°C, forms a mixture of 2-amino-(**12**) and 4-amino-(**13**) adducts in the ratio 3:1, but after oxidative aromatization of these adducts at the same temperature the products **14** and **15** are obtained in 53 and 10% yields, respectively.



Scheme 9 Modified procedures for oxidative amination

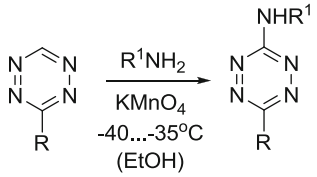
The aza group activation effect in the oxidative amination of azines is less than that of the nitro group. As an illustration: the reaction of 4-nitroquinoline and liquid ammonia in the presence of $KMnO_4$ produced 3-amino-4-nitroquinoline only in 86% yield [52]. Oxidative amination of 5-nitroquinoline gave 6-amino derivative in 33% yield [53].

Liquid ammonia and potassium permanganate system were also effectively applied to introduce an imino group in the highly electron-deficient *N*-alkylazinium salts [30, 39].

Oxidative amination of 2-amino-3,5-dinitropyridine-1-oxide has recently been performed by using ammonia (gas), bubbling into a solution of this substrate and $KMnO_4$ in DMSO (Scheme 9) [54]. 2-R-1,3,5-Triazapyrenes have been aminated with aqueous ammonia in dioxane in the presence of $K_3[Fe(CN)_6]$ to give the corresponding 6-amino derivatives in 89–95% yield (Scheme 9) [55]. The reaction can also be carried out without dioxane as co-solvent, but in this case it requires a more time.

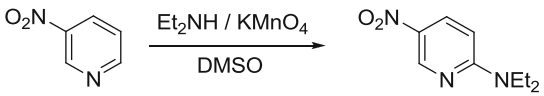
3.2 Alkylamination

Advances in oxidative amination of azines stimulated many researchers to study oxidative methylamination of nitroazines, such as 3-nitropyridines, nitroquinolines, nitronaphthiridines, nitroquinoxalines, by using the system $MeNH_2/KMnO_4$ [30, 56]. Moreover, both procedures, amination and methylamination, have successfully been applied in the series of 1,3-dinitrobenzenes [57, 58]. In general, nitroaromatic compounds are more active in these reactions than azines containing the same



R	R^1	%
Me	Et	76
t-Bu	Et	81
Ph	Et	59
Me	Bu	35
t-Bu	Bu	47
Ph	Bu	44
Me	C_8H_{17}	35
t-Bu	C_8H_{17}	58
Ph	C_8H_{17}	38
Ph	*i*-Pr	18

Scheme 10 Oxidative alkylamination of *sym*-tetrazines



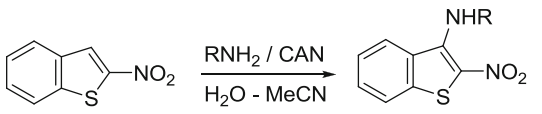
Scheme 11 Oxidative alkylamination of 3-nitropyridine in DMSO solution

number of aza groups. For a recent review on the S_N^H-amination of nitroaromatic hydrocarbons see [38].

The reactions of azines with other alkylamines and $KMnO_4$ proved to be less successful. Yields of alkylamination products have been established to decrease gradually, while the alkyl chain becomes longer and more branched. In particular, it is nicely demonstrated by the data on alkylamination of tetrazines (Scheme 10) [49]. This phenomenon can possibly be explained by a lower solubility of $KMnO_4$ in higher alkylamines.

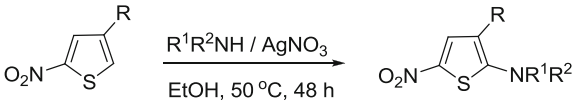
In order to improve the solubility of $KMnO_4$ in alkylamines, especially secondary ones, polar solvents were used. For instance, treatment of 3-nitropyridine with diethylamine and $KMnO_4$ in DMSO gave 6-diethylamino derivative in 60% yield, while without DMSO the reaction did not occur at all (Scheme 11) [59]. As isolation of the target product in the presence of DMSO is rather complicated, alkylamination of 1,2,4-triazine-4-oxides with dialkylamines (such as Me_2NH, Et_2NH, pyrrolidine, piperidine, and morpholine) and $KMnO_4$ can be carried out in acetone, as co-solvent [60].

Since alkylamines are more sensitive to oxidation than liquid ammonia, numerous attempts to find an appropriate oxidant (instead of $KMnO_4$), possessing a higher selectivity towards σ^H-complexes, have been undertaken. For example, alkylaminations of 2-nitrobenzothiophene with primary amines have been performed in various solvents in the presence of such oxidants as $AgNO_3$, H_2O_2, *t*-BuOOH, MnO_2, or *N*-methylmorpholine N-oxide. However, yields of 3-alkylamino derivatives proved to be very low, varying from 0 to 14% [61]. The best results were obtained with ceric ammonium nitrate (CAN) in water−acetonitrile system (Scheme 12). Unfortunately, CAN did not work properly in the reactions with secondary alkylamines.



R	%
Pr	57
i-Pr	59
Bu	42
cyclo-C_6H_{11}	54
Ph(Me)CH	66
CH_2=CH-CH_2	41
$HOCH_2CH_2$	42
$MeO_2CCH_2CH_2$	20

Scheme 12 Oxidative alkylamination of 2-nitrobenzo[*b*]thiophene with CAN



R = Me, CH(OH)Me, CH(OMe)Me

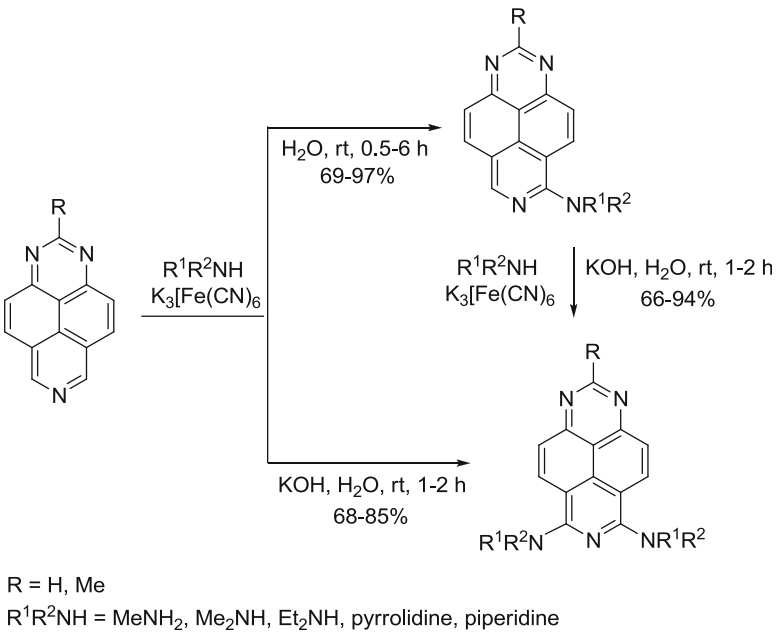
R^1R^2NH = Me_2NH, Et_2NH, $MePhCH_2NH$, pyrrolidine, morpholine, piperidine

Scheme 13 Oxidative alkylamination of 4-R-2-nitrothiophenes with $AgNO_3$

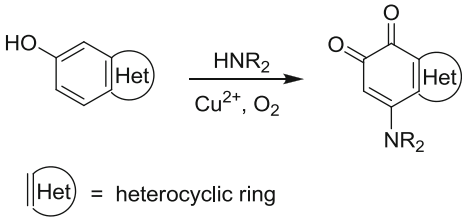
In contrast, alkylamination of 4-R-substituted 2-nitrothiophenes in the presence of silver nitrate proved to be possible only in cases of secondary amines (Scheme 13) [62]. Yields of 5-nitro derivatives formed as the sole product were ranged from 10 to 75%. It is noteworthy that oxidants other than $AgNO_3$, in particular, CAN or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), gave worse results.

1,3,7-Triazapyrenes have been shown to react with an excess of primary and secondary amines in the presence of $K_3Fe(CN)_6$ in water solution at room temperature giving rise to the corresponding 6-alkyl(dyalkyl)amino-1,3,7-triazapyrenes (Scheme 14) [63]. In the cases of secondary amines (not primary) addition of KOH to the reaction mixture allows obtaining products of double amination into positions 6 and 8.

Air oxygen can also play the role of oxidant in the amination reactions. It is well known that 1,4-benzoquinone reacts with aliphatic amines in the presence of copper acetate to give 2,5-bis(dialkylamino)-1,4-benzoquinones in good yields [64]. The reaction mechanism involves nucleophilic 1,4-addition followed by oxidation of intermediate aminohydroquinones with air oxygen. The reactions of this type, which are also inherent to *ortho*-quinones, have been reviewed earlier [65, 66]. It is interesting that amination is also possible in case of some heterocyclic phenols, which are first converted in situ into the corresponding *ortho*-quinones. This approach has successfully been exploited to aminate *ortho*-quinones generated from quinolines, indoles, acridines, isoquinolines, quinoxalines, benzofurans, and benzothiazoles (Scheme 15) (for review, see [65, 66]).



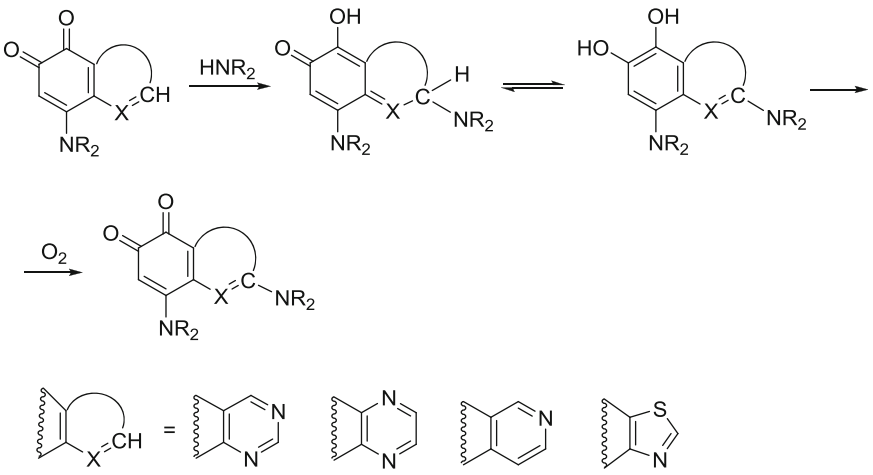
Scheme 14 Oxidative alkylamination of 1,3,7-triazapyrenes with $K_3Fe(CN)_6$



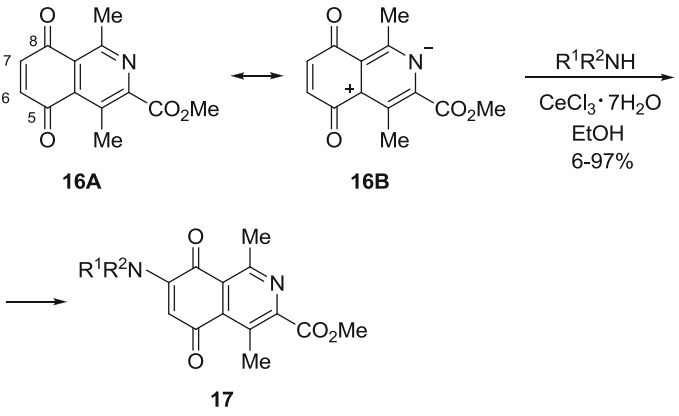
Scheme 15 Oxidative alkylamination of heterocyclic 1,2-quinones

Sometimes the reaction proceeds further, thus involving a heterocyclic ring (Scheme 16). Heterocyclic 1,4-quinones demonstrate a similar reactivity [67].

It is clear that in the reactions of heterocyclic quinones with amines the formation of regioisomeric products is possible because of non-equivalency of the quinone carbonyl groups. The amination direction depends on the substitution pattern in the starting quinone substrate. For example, isoquinoline-5,8-dione **16** reacts with amines in the presence of $CeCl_3 \cdot 7H_2O$ to produce 7-alkylamino derivatives **17** as the sole products (Scheme 17) [68]. This high regioselectivity can be attributed to the C-5 carbonyl fragment, which appears to be a more electron-deficient one due to the electron-withdrawing effect of the aza group, as reflected by the resonance structure **16B**. This effect is spread mainly at C-7, rather than at C-6 atom, thus directing a nucleophilic attack. 3,4-Dihydrophenanthridine-1,7,10(2*H*)-trione demonstrates a rather poor regioselectivity in this reaction, while its 6-methyl analogue is aminated selectively into position 8 [69].



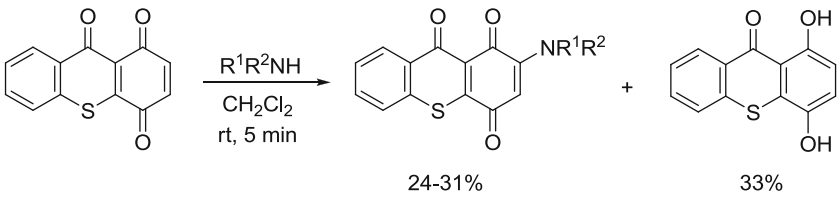
Scheme 16 Double oxidative alkylamination of heterocyclic *ortho*-quinones



Scheme 17 Regioselective oxidative alkylamination of isoquinoline-5,8-dione **16**

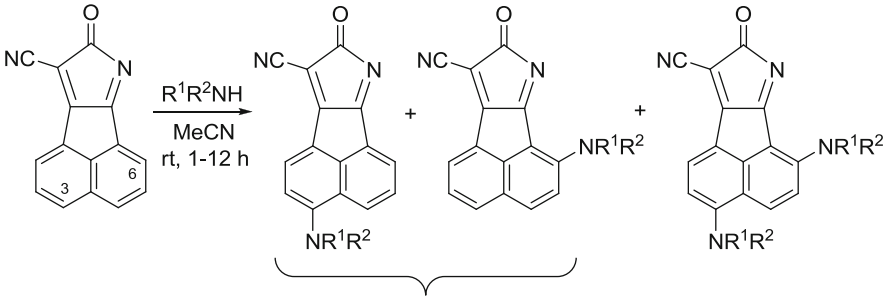
In some amination reactions the starting aromatic substrate itself can act as an acceptor of the hydride ion. For example, 1*H*-thioxanthene-1,4,9-trione reacts with alkylamines in CH_2Cl_2 (toluene or DMSO) to give the corresponding 2-amino compound in addition to 1,4-dihydroxy-9*H*-thioxanthen-9-one (Scheme 18) [70].

In a similar manner 8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrole-9-carbonitrile reacts with primary alkylamines under rather mild conditions to give the corresponding 3-alkylamino derivatives in 40–45% yields (Scheme 19) [71, 72]. The reaction with secondary cyclic amines is less selective and, in addition to 3-amino derivatives, 6-substituted and 3,6-disubstituted products are also formed. Both monoamines can



R^1R^2NH = *cyclo*-C_6H_{11}, piperidine

Scheme 18 1*H*-Thioxanthene-1,4,9-trione acting as both substrate and oxidant in the alkylamination reaction

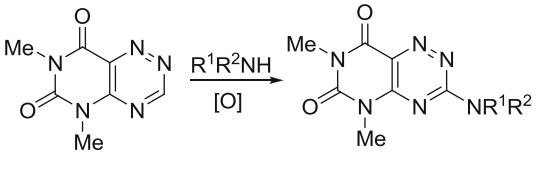


R^1R^2NH = *i*-$PrNH_2$, $BuNH_2$, $HOCH_2CH_2NH_2$, $H_2N(CH_2)_3CO_2Et$, $H_2N(CH_2)_2NEt_2$, piperidine, morpholine, thiomorpholine, N-methylpiperazine

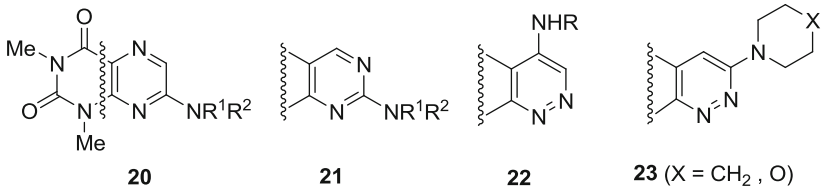
Scheme 19 Alkylamination of 8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrole-9-carbonitrile

be aminated repeatedly into 3,6-diamino-8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrole-9-carbonitriles. The difference in the reactivity between secondary and primary amines may be assigned to a steric hindrance caused by the *peri* hydrogen atom. Oxidation of the intermediate σ^H-complexes in this reaction seems to be carried out by both air oxygen and the starting aromatic substrate. Indirectly, this follows from moderate yields of the amination products. The notable feature of this reaction is a distant location of the activating electron-withdrawing groups which are quite far in the molecule from the C–H hydrogen to be substituted.

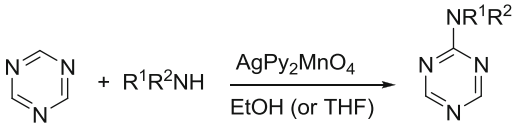
Perhaps, the best oxidant from those ever used in the alkylamination reactions in the series of azaaromatics is the complex of silver permanganate with pyridine $AgPy_2MnO_4$ (Py = pyridine). It is well soluble in alkylamines and can easily be prepared by mixing aqueous solutions of $KMnO_4$, pyridine, and silver nitrate in stoichiometric amounts [73]. It remains stable at storage in a refrigerator, although it decomposes gradually on heating. Oxidative alkylamination of isofervenulin **18** and its analogues can be regarded as a very indicative example [74]. Indeed, amination of **18** with primary alkylamines in the presence of $KMnO_4$ results in the formation of amines **19** in high yields. At the same time, the reaction with diethylamine fails to yield any products, because of a very low solubility of $KMnO_4$



R^1R^2NH	[O]	%
NH_3	$KMnO_4$	75
$MeNH_2$	"	90
$EtNH_2$	"	81
t-$BuNH_2$	"	94
Me_2NH	"	89
Et_2NH	"	0
Et_2NH	$AgPy_2MnO_4$	76
NH	"	87
O NH	"	93



Scheme 20 Oxidative alkylamination of isofervenulin and its deazaanalogs

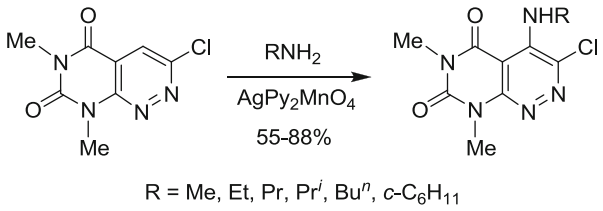


R^1R^2NH	%
NH_3	30
$MeNH_2$	26
i-$PrNH_2$	33
$BuNH_2$	56
n-$C_5H_{11}NH_2$	50
NH	39
O NH	63

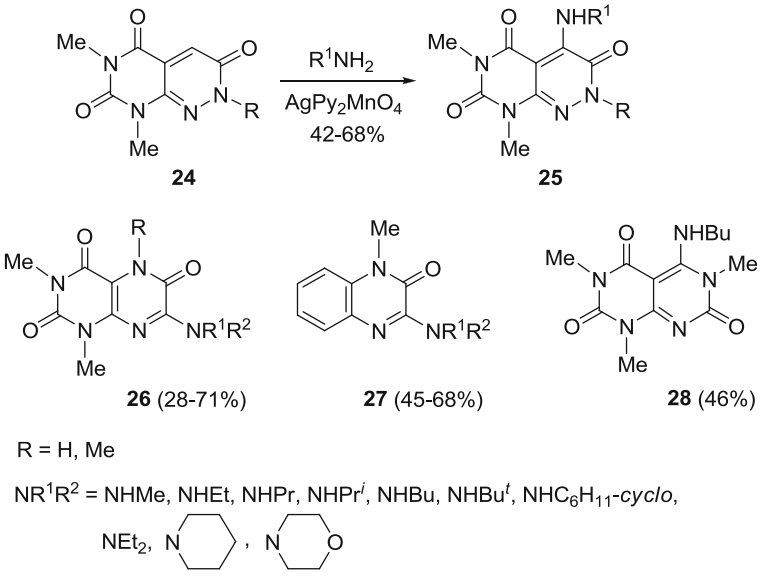
Scheme 21 Oxidative amination and alkylamination of 1,3,5-triazine

in this amine (Scheme 20). In contrast, amination of isofervenulin **18** with diethylamine and other secondary amines in the presence of $AgPy_2MnO_4$ affords the corresponding 3-alkylamino derivatives in 76–93% yields. Similar alkylaminations of diazine analogues of isofervenulin with various primary and secondary alkylamines give rise to amino compounds **20–23** (for review, see [35]).

1,3,5-Triazine is known to be a very vulnerable for a nucleophilic attack, for instance, it is decomposed by even a cold water. Low temperature reactions of 1,3,5-triazine with ammonia or alkylamines and $AgPy_2MnO_4$ in ethanol or THF as a co-solvent (to avoid freezing of alkylamines) gave hardly accessible 2-amino- and 2-alkylamino-1,3,5-triazines in good to moderate yields (Scheme 21) [75]. It is worth noting that alkylamination of the parent 1,3,5-triazine did not occur in the presence of $KMnO_4$.



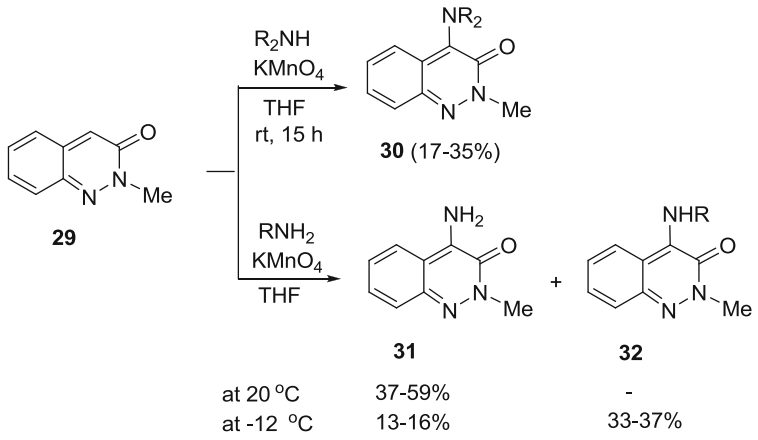
Scheme 22 Alkylamination of 3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione



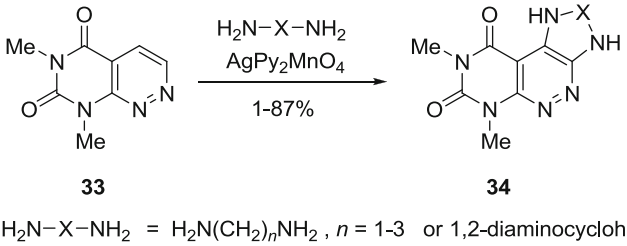
Scheme 23 Oxidative alkylamination of some condensed diazinones

By using $AgPy_2MnO$ selective alkylamination of a number of azaaromatics bearing nucleophile-sensitive groups, e.g., 3-chloro-6,8-dimethylpyrimido[4,5-*c*]-pyridazine-5,7(6*H*,8*H*)-dione (Scheme 22) [76] and 6,8-dimethylpyrimido[4,5-*c*] pyridazine-3,5,7(2*H*,6*H*,8*H*)-triones **24** have been carried out (Scheme 23) [77]. Alkylaminopyrazinones **26**, **27** and alkylaminopyrimidinones **28** have been obtained similarly [77]. The direct alkylamination of azinones is rather important due to the well-known data on antiviral activity of amino derivatives of this family (acyclovir, racivir, lamivudine, zalcitabine, and some other) [1].

The oxidative alkylamination of 2-methyl-3(2*H*)-cinnolinone **29** by action of secondary alkylamines in the presence of $KMnO_4$ in THF under ambient conditions proceeds rather smoothly, leading to the formation of the expected 4-alkylamino-2-methyl-3(2*H*)-cinnolinones **30** (Scheme 24) [78]. Interestingly, the analogous reaction with primary alkylamines is accompanied by a partial or complete



Scheme 24 Oxidative alkylamination of 2-methyl-3(2*H*)-cinnolinone

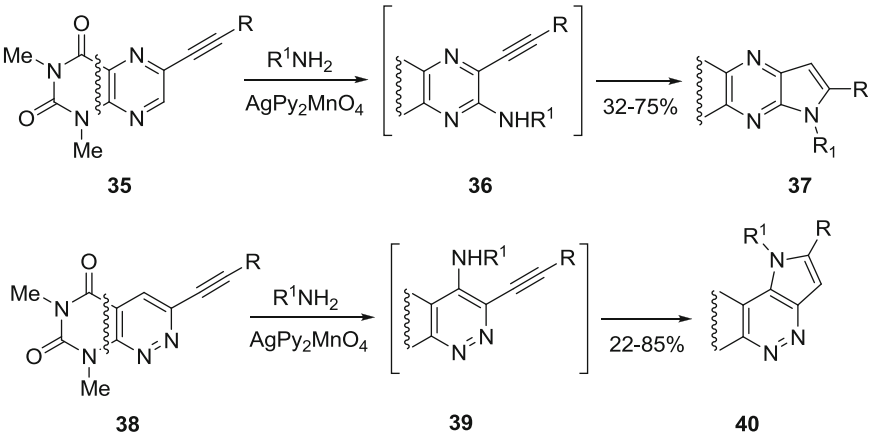


Scheme 25 Tandem oxidative alkylamination of pyrimidopyridazine substrate

(depending on temperature) *N*-dealkylation of the entering alkylamino group. It has been shown that the transformation **29**→**31** involves oxidation of alkylaminocinnolinones **32** into the corresponding azomethines, followed by their hydrolysis. The exclusive formation of 4-*tert*-butylaminocinnolinone on reacting **29** with *t*-$BuNH_2$ and $KMnO_4$ can be considered as conclusive evidence of this mechanism. Notably, replacing $KMnO_4$ with $AgMnO_4$ resulted in enhancement of yields of both alkylamino and amino products, thus changing their ratio in favor of **31**.

Also use of $AgPy_2MnO_4$ as oxidant allowed to perform for the first time the tandem S_N^H-alkylamination of pyrimidopyridazine **33** by action of aliphatic α,ω-diamines, thus affording polynuclear heterocycles **34** (Scheme 25) [79].

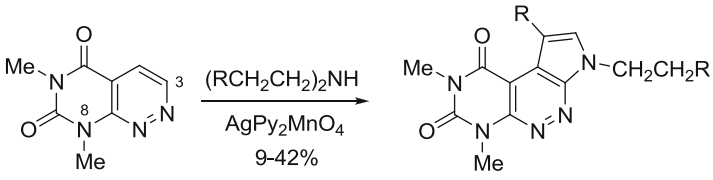
Recently, it has been demonstrated that involvement of oxidative alkylamination as a step into cascade transformations allows the synthesis of rather complicated compounds, which otherwise are hardly accessible. For instance, alkylamination of alkynyldiazines **35** and **38** in the presence of $AgPy_2MnO_4$ gave fused pyrroles **37**



R = Ph, *n*-C_6H_{13}, $SiMe_3$

R^1 = Et, Pr, *i*-Pr, Bu, *t*-Bu, *cyclo*-C_6H_{11}

Scheme 26 Oxidative alkylamination of alkynyldiazines leading to spontaneous closure of the pyrrole ring

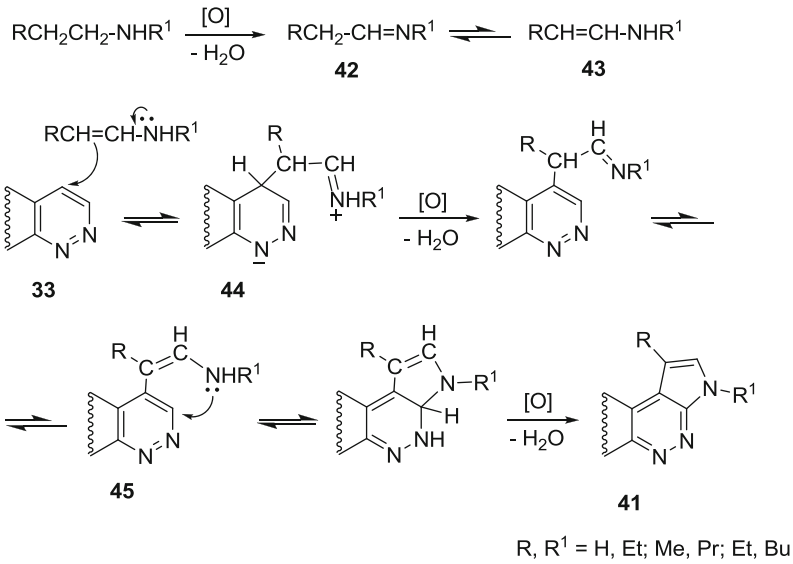


R = H, Me, Et

Scheme 27 Annelation of the pyrrole ring due to oxidative alkylamination of pyrimidopyridazine **33**

and **40**, most likely through spontaneous cyclization of the initially formed alkylamino derivatives **36** and **39** (Scheme 26) [80, 81]. It is a common point of view that cyclizations of this kind are promoted by bases, electrophiles, or transition metal complexes. Apparently, in transformations discussed above both alkylamine and the silver complex can act as such catalysts.

It has already been mentioned that oxidative alkylamination of pyrimidopyridazine **33** with primary alkylamines yields 4-alkylamino derivatives **22** (see Scheme 20). However, in the reactions of **33** with acyclic secondary amines in the presence of $AgPy_2MnO_4$, fused pyrroles **41** proved to be the sole products (Scheme 27) [82].

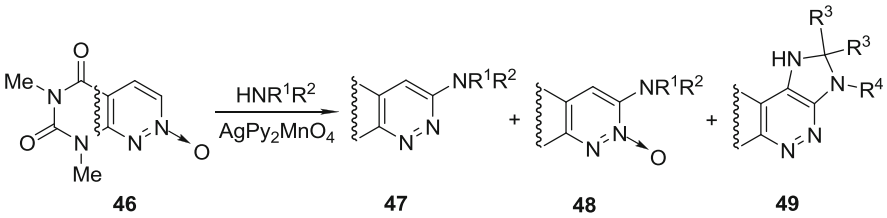


Scheme 28 Proposed mechanism for the cascade formation of pyrroles **41**

Acyclic dialkylamines are not very reactive as nucleophiles in the oxidative alkylamination, however they are very prone to oxidation and, therefore, they are capable for unexpected behavior. Presumably, transformation **33**→**41** starts from oxidation of dialkylamine into imine **42**, that is in equilibrium with enamine **43** (Scheme 28). The latter, as bifunctional *C*,*N*-nucleophile, attacks C-4 atom of the pyridazine ring to form σ^H-adduct **44**, which then undergoes oxidative aromatization. Subsequent intramolecular oxidative amination of the intermediate **45** yields pyrrole derivative **41**. The participation of imines in this process has been confirmed experimentally. In the presence of $AgPy_2MnO_4$, pyrimidopyridazine **33** reacts with authentic aldimines and ketimines **42** to give pyrroles **41**. Transformation **33**→**41** represents not only a rare example of the tandem S_N^H–S_N^H processes but also a novel route to fused pyrroles.

Pyrimidopyridazine *N*(2)-oxide **46** reacts with various alkylamines and $AgPy_2MnO_4$ to give a mixture of 3-alkylamino derivatives **47** and **48** in 50–68% yields (Scheme 29), the latter being predominant ones and the former representing products of the *cine*-substitution reaction (see Sect. 5.1) [83]. Interestingly, amination of compound **46** with cyclohexylamine or isopropylamine affords the corresponding 3-amino derivatives **47e**,**g** and imidazolines **49a**,**b** in ~5% yields [84, 85].

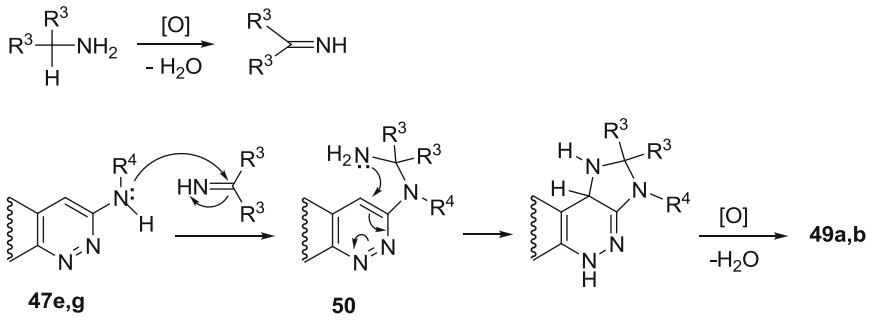
A plausible mechanism for annelation of the imidazoline ring includes the following steps (Scheme 30): (1) oxidation of cyclohexylamine (or isopropylamine) into the corresponding imine, (2) addition of 3-alkylaminopyridazine **47** to the imine C=N bond, which leads to the *gem*-diamine **50**, and (3) intramolecular oxidative alkylamination (**50**→**49**). The formation of imidazolines **49a**,**b** only with cyclohexylamine and isopropylamine can be explained by a comparative ease for



47, **48**: NR^1R^2 = NH_2 (**a**), NHMe (**b**), NHEt (**c**), NHPr (**d**), $NHPr^i$ (**e**), NHBu (**f**), NHC_6H_{11}-*cyclo* (**g**), $NHCH_2Ph$ (**h**), NMe_2(**i**), piperidino (**j**), morpholino (**k**)

49: R^3, R^3 = -$(CH_2)_5$- , R^4 = *c*-C_6H_{11} (**a**), R^3 = Me, R^4 = $CHMe_2$ (**b**)

Scheme 29 Oxidative alkylamination of pyrimidopyridazine *N*(2)-oxide **46**



47: R^4 = $NHPr^i$ (**e**), NHC_6H_{11}-*cyclo* (**g**)

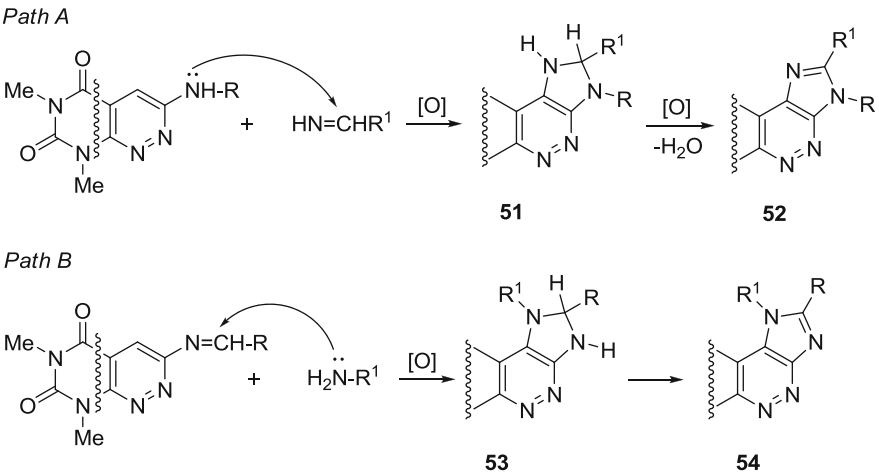
49: R^3, R^3 = -$(CH_2)_5$- , R^4 = *cyclo*-C_6H_{11} (**a**), R^3 = Me, R^4 = $CHMe_2$ (**b**)

Scheme 30 Proposed mechanism for the formation of imidazolines **49**

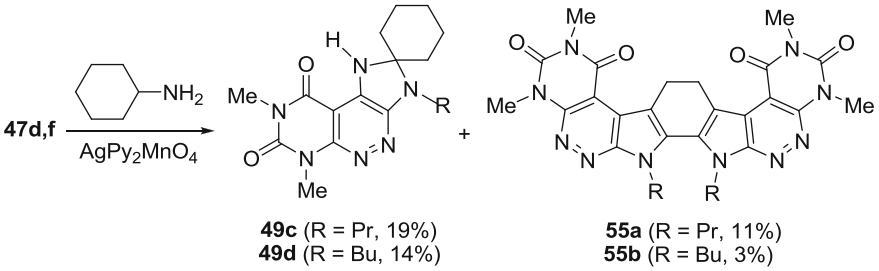
the oxidation of these amines and a relative stability of the corresponding imines. This mechanism was confirmed by the experiment, in which 3-cyclohexyl amino compound **47g** was allowed to react with cyclohexylamine and $AgPy_2MnO_4$ to give imidazoline **49a** in 65% yield.

Similar heterocyclizations have been performed in the series of other 3-alkylaminopyrimidopyridazines **47** and primary amines [85]. Their course is likely determined by relative abilities of reactants to undergo oxidative transformations (Scheme 31). Depending on whether the primary amine (*Path A*) or the amino moiety in azaaromatics (*Path B*) is oxidized, two types of isomeric imidazolines **51** and **53** are formed.

The transformation shown in Scheme 30 corresponds to the *Path A*. In a similar manner the reactions of 3-propylamino and 3-butylaminopyridazines **47d**,**f** with cyclohexylamine in the presence of oxidant gave imidazolines **49c**,**d**, however, in



Scheme 31 Two possible pathways for the formation of imidazolines from compounds **47**



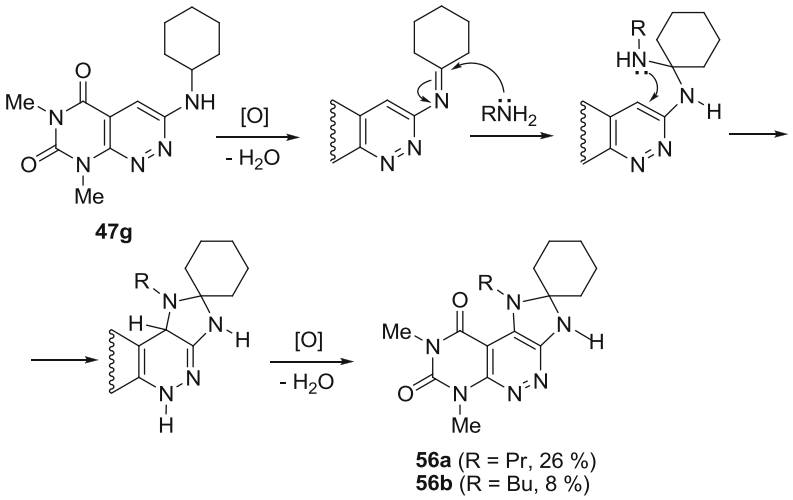
Scheme 32 Transformations of compounds **47d**,**f** in cyclohexylamine /$AgPy_2MnO_4$ system

these two particular cases small amounts of unusual polycyclic compounds **55a**,**b** were isolated (Scheme 32). The *Path A* is also realized when compounds **47d**,**g** react with benzylamine, with the exception that imidazolines **51** are then oxidized into imidazoles **52** (R^1 = Ph).

Another combination of reagents, in which 3-cyclohexylaminopyrimidopyridazine **47g** is used as substrate and propylamine or butylamine as nucleophile, affords imidazolines **56a**,**b**, isomeric to compounds **49c**,**d**. Apparently, the process starts with oxidation of 3-alkylamino group of the starting aromatic substrate and proceeds as shown in Scheme 33.

3-Benzylamino compound **47h** reacts with alkylamines in a similar way to afford imidazoles **54** in 18–64% yields. In the reaction of **47h** with cyclohexylamine polycyclic compound **55c** (R = $PhCH_2$) is also formed in 8% yield. Interestingly, 3-alkylamino derivatives **47c**,**d**,**f** can also be transformed into imidazoles **54** on treatment with the corresponding alkylamine/$AgPy_2MnO_4$ system.

Presumably, a course of the abovementioned reactions is determined by amino functionality, which is oxidized most easily. In this respect, one can make the

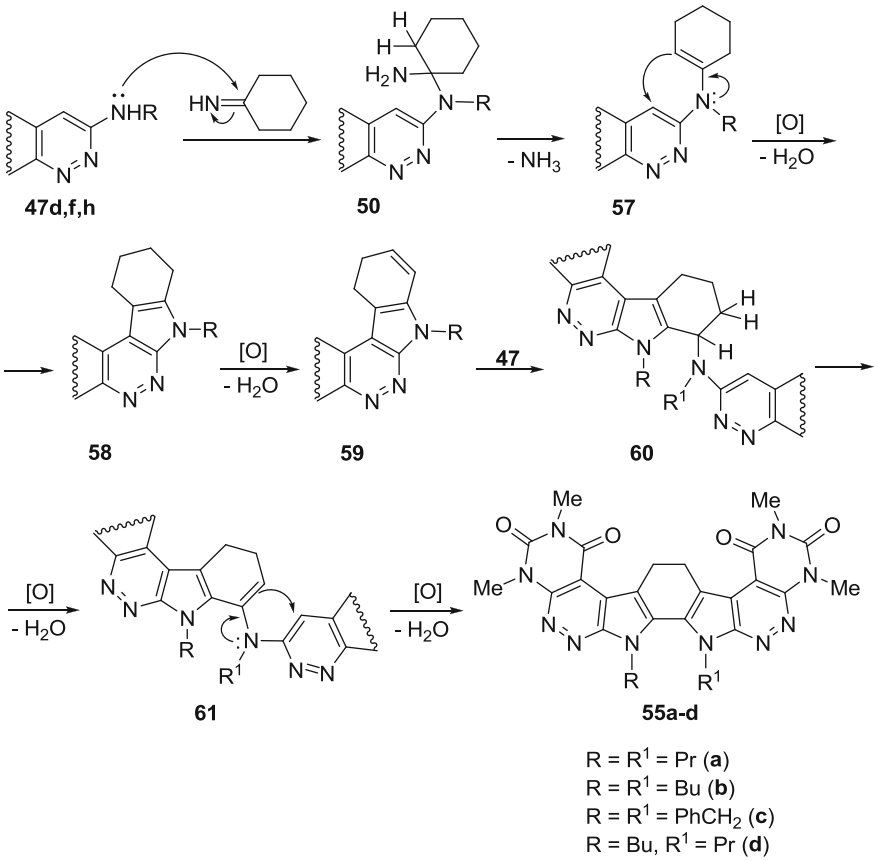


Scheme 33 Transformations of compound **47g** by action of $RNH_2/AgPy_2MnO_4$

following assumptions. Benzylamine itself and 3-benzylamino group in compound **47h** are most readily transformed into the corresponding imines. In the absence of benzylamine fragment, the cyclohexylamino group becomes the mostly reactive towards oxidant. If both reagents contain no benzylamino or cyclohexylamino group, the cyclization is initiated by oxidation of 3-alkylamino group in compound **47**. It is worth noting that this kind of heterocyclizations, leading to imidazole or imidazoline ring closure, has not so far been known.

The formation of heptacyclic compounds **55** in the reactions of 3-alkylamino pyrimidopyridazines **47** with cyclohexylamine is of particular interest. The process seems to be triggered by conversion of cyclohexylamine into cyclohexanone imine, followed by the cascade of heterocyclizations, shown in Scheme 34. It involves: (1) addition of 3-alkylaminopyrimidopyridazine **47** to the C=N bond of cyclohexanone imine, (2) elimination of ammonia molecule from *gem*-diamine **50** leading to enamine **57**, (3) oxidative S_N^H-cyclization of the latter into tetrahydroindole **58**, (4) oxidation of **58** into alkene **59**, (5) addition of the starting compound **47** at the C=C bond of alkene **59**, affording the intermediate **60**, and (6) oxidation of the latter into enamine **61**, and, finally, oxidative S_N^H-cyclization **61**→**55**. Participation of tetrahydroindoles **58** in this transformation has been confirmed experimentally: treatment of preliminary prepared compounds **58** (R = Pr, Bu, $PhCH_2$) with equimolar quantities of the corresponding 3-alkylaminopyrimidopyridazines **47d**,**f**,**h** in cyclohexylamine/$AgPy_2MnO_4$ increases yields of compounds **55a**–**c** up to 48–50%. The latter reaction allows obtaining unsymmetrical *N*-substituted compounds **55**. For instance, tetrahydroindole **58** (R = Bu) reacts with 3-propylamino derivative **47d** to give **55d**.

3-Alkylaminopyrimidopyridazines **47d**,**f**,**h** react with cycloheptylamine in a similar way, yielding cycloheptano-*bis*(pyrrolopyrimidopyridazines) **63** and

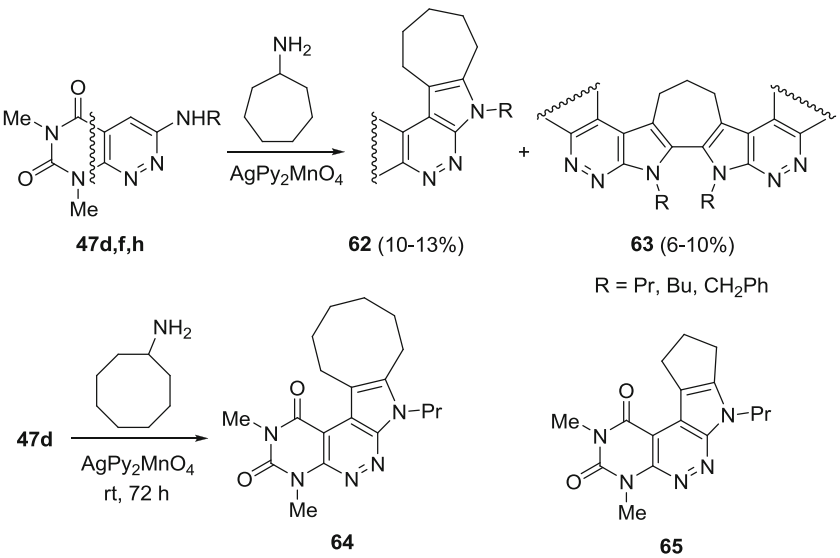


Scheme 34 A plausible mechanism for the formation of compounds **55**

cycloheptapyrroles **62** (Scheme 35) [86]. In the reaction of **62** with pyridazines **47**, yields of compounds **63** are increasing up to 25–30%. Reactions of **47d** with cyclooctylamine and cyclopentylamine in the presence of $AgPy_2MnO_4$ gave cyclooctapyrrole **64** and cyclopentapyrroles **65**, as the final products.

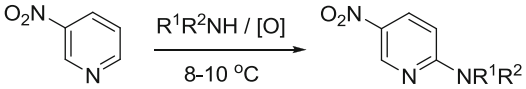
Thus, in the S_N^H-amination reactions an oxidant may take part not only in aromatization of the intermediate σ^H-adducts but also in chemical modification of nucleophile, substrate, and intermediates. This opens up new horizons for obtaining compounds, which are otherwise not easily accessible. In this regard, the one-pot synthesis of compounds **55** and **63**, in which six new bonds are subsequently formed, appears to be a good example of the most complex currently known S_N^H-heterocyclizations (for review on this topic, see [34]).

The efficiency of a number of oxidants ($KMnO_4$, $AgPy_2MnO_4$, $AgMnO_4$, and CAN) was compared on the basis of the alkylamination reaction of 3-nitro-pyridine (Table 1) [87]. With the exception of diethylamine, all other alkylamines gave good



Scheme 35 Transformations of compounds **47** in cycloalkylamine/$AgPy_2MnO_4$ system

Table 1 Influence of the nature of an oxidant on alkylamination of 3-nitropyridine



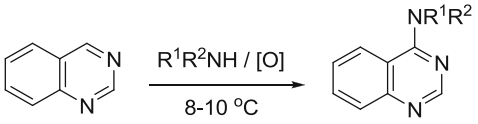
	Yields (%)			
Alkylamine	$KMnO_4$	$AgPy_2MnO_4$	$AgMnO_4$	CAN
i-$PrNH_2$	91	83[a]	–	22
$BuNH_2$	93	91[a]	–	–
n-$C_5H_{11}NH_2$	82	91[a]	–	–
$PhCH_2NH_2$	0	64[a]	–	–
Pyrrolidine	50	94	–	–
Piperidine	70	95	–	–
Morpholine	71	96	–	15
Homopiperidine	0	82	–	–
Et_2NH	0	14–20	9	–

[a]Diamino derivatives (2–10%) were also isolated

yields of alkylamination products in the presence of $AgPy_2MnO_4$. Potassium permanganate was not a proper oxidant for the reactions of 3-nitropyridine with benzylamine, homopiperidine, or diethylamine. Also $AgMnO_4$ was shown to be not suitable, although it gave a low yield of the amination compound with diethylamine, while CAN proved to be not efficient oxidant.

The most distinct difference between $KMnO_4$ and $AgPy_2MnO_4$ was exhibited in the alkylamination of quinazoline (Table 2) [87]. Unlike $AgPy_2MnO_4$ and

Table 2 Effect of an oxidant on alkylamination of quinazoline



	Yields (%)		
Alkylamine	$KMnO_4$	$AgPy_2MnO_4$	$AgMnO_4$
i-$PrNH_2$	8	86	–
$BuNH_2$	39	93	81
n-$C_5H_{11}NH_2$	6	96	–
c-$C_6H_{11}NH_2$	5	87	–
$PhCH_2NH_2$	0	81	78
Pyrrolidine	Trace	31	–
Piperidine	Trace	68	–
Morpholine	2	96	–
Homopiperidine	0	32	–
Et_2NH	0	28	–

$AgMnO_4$, less soluble $KMnO_4$ failed in many cases to take part in this reaction. An interesting observation has been made upon using $AgMnO_4$ in the reaction. Although 4-alkylaminoquinazolines were obtained in good yields, the reaction mixture turned to be characteristic purple not immediately upon addition of oxidant, but after some time. This may be explained by a gradual formation of more soluble complexes $Ag(alkylamine)_2MnO_4$, which then act as oxidants.

In order to understand this phenomenon, the mechanism of oxidative alkylamination of 3-nitropyridine, 1,3-dinitrobenzene, and quinazoline with butylamine and pyrrolidine has been investigated [88].

In all cases, the corresponding σ^H-adducts were registered at low temperatures by NMR spectroscopy. As expected, for all substrates studied the concentration of σ^H-adducts with pyrrolidine at a given temperature was larger than that with a less nucleophilic butylamine. Measurement of the amount of σ^H-adduct at different temperatures enabled the construction of van't Hoff plots. ΔH_r° and ΔS_r° for σ^H-adduct formation were derived of these plots for all reactions. On the basis of the competitive kinetic isotope effect experiments, it was shown that the rate-limiting step is oxidation of the intermediate σ^H-adducts. Accordingly, concentrations of both σ^H-adduct and oxidant influence on overall rate of the reaction. Since quinazoline forms more stable σ^H-adducts with amines than mononuclear 3-nitropyridine does, quinazoline adducts are supposed to be more difficult to oxidize, and they require a higher concentration of oxidant in the reaction mixture. That is why the efficiency of $KMnO_4$ (poor solubility in amines) and $AgPy_2MnO_4$ (good solubility in amines) is so different just in case of quinazoline. The assumption that Ag^+ ion may play an active role and possibly promotes the formation of σ^H-adducts (due to its coordination with the aza group) or their oxidation did not get an experimental support.

The ^{1}H NMR spectroscopy has been exploited to estimate thermodynamic characteristics and effects of additives for σ^H-adduct formation. The addition of such additives, as salts $AgNO_3$ and tetrabutylammonium chloride (TBACl), has been shown to have a major impact on the ΔS_r^o value and consequently on the σ^H-adduct concentration. These findings explain the preference of $AgPy_2MnO_4$ for the oxidative alkylamination; apparently, besides a higher concentration of MnO_4^- in a reaction solution, $AgPy_2MnO_4$ facilitates the formation of σ^H-adducts, thus increasing the overall rate of the reaction. In cases where a low conversion is observed in the reaction with $KMnO_4$, a combination of $AgNO_3/KMnO_4$ or $TBACl/KMnO_4$ provides better yields, similar to those obtained with $AgPy_2MnO_4$. The combination $TBACl/KMnO_4$ appears to be especially interesting, since it is based on more cheaper and environmentally friendly reagents. Tetrabutylammonium permanganate (TBAP), a more soluble analogue of $KMnO_4$, has also been tested and proved to be a suitable alternative for $TBACl/KMnO_4$.

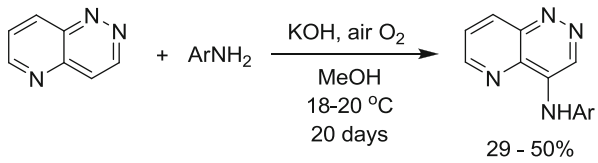
3.3 Arylamination

Direct incorporation of arylamino fragments into heteroaromatic compounds has some features. Unfortunately, the oxidative amination and alkylamination procedures cannot be applied for arylamination, because of a reduced *N*-nucleophilic character, a high sensitivity of aromatic amines towards oxidation, and a low stability of arylamino-σ^H-adducts. These factors explain why S_N^H-arylamination reactions are still rare. A vast majority of the known examples are intramolecular reactions, which are performed in the presence of mild oxidants, such as sulfur, chloranil, or nitrobenzene (for review, see [34]). In some cases, air oxidation of the intermediate σ^H-complexes has been observed. In the series of nitroarenes the nitro group often acts as the hydride ion acceptor. Similarly, in arylamination of azaaromatics the cyclic C=N bond can intercept the hydride ion.

Only a few intermolecular oxidative arylamination reactions in the heterocyclic series have so far been reported. 5-Azacinnoline, 1,2,4-triazines, 3-nitropyridines, and heterocyclic quinones are among those compounds which react with anilines or hetarylamines in the presence of a strong base. In fact, in order to perform these reactions metal salts of arylamides are needed as nucleophiles. For instance, interaction of 5-azacinnoline with arylamines in the presence of potassium hydroxide demands 20 days to complete the process with crucial access to air oxygen (Scheme 36) [89].

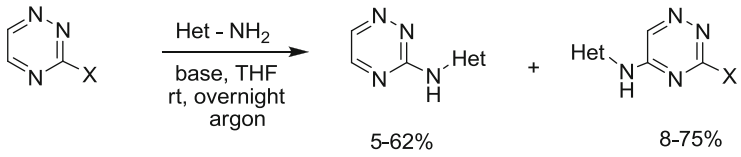
Contrary to that, hetarylamination of 3-X-1,2,4-triazines proceeds smoothly under inert atmosphere without external oxidant (Scheme 37) [90], although there are no doubts that it is the starting triazine, which plays the role of oxidant.

3-Nitropyridines have been shown to react with 2-, 3-, or 4-aminopyridines in the presence of LiHMDS (or LDA) in THF without isolation of the reaction mixture from air oxygen (Scheme 38) [91]. In other studies 3-nitropyridine was allowed



Ar = Ph, *p*-Tol, 4-$MeOC_6H_4$, 4-ClC_6H_4, naphthalen-1-yl, pyridin-3-yl

Scheme 36 Oxidative arylamination of 5-azacinnoline

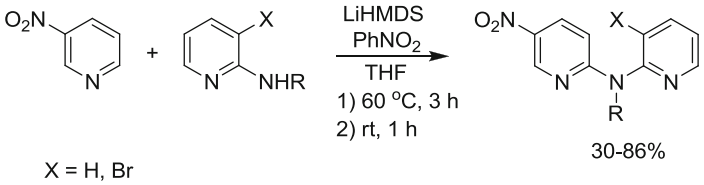


base: HTMP/*t*-BuOK/*n*-BuLi; HTMP/*t*-BuONa/*n*-BuLi

X = OMe, SMe, SBu-*t*

Het = pyridin-2-yl, pyrazin-2-yl, 1,2,4-triazin-3-yl, 5-nitropyrimidin-2-yl, 3-nitro-1,2,4-triazol-5-yl, tetrazol-5-yl, 4-nitropyrazol-5-yl

Scheme 37 Oxidative arylamination of 1,2,4-triazines



X = H, Br

R = H, Me, Bu

Scheme 38 Oxidative arylamination of 3-nitropyridines

to react with lithium arylamides (prepared by treatment of 2-aminopyridine, 2-aminoquinoline, aniline, or phenylamidine with BuLi in THF at −78°C) under anaerobic conditions [92]. In these cases, yields of arylamination products did not exceed 39%. Use of nitrobenzene as co-solvent might improve yields due to its ability to oxidize σ^H-adducts. It is interesting to note that when the reaction of 3-nitropyridine with 2-aminopyridine was carried out in the presence of 1,3-dinitrobenzene, the (pyridin-2-yl)amino derivatives of both 3-nitropyridine and 1,3-dinitrobenzene were obtained in 13 and 28% yields, respectively [92]. This is a clear indication that 1,3-dinitrobenzene is more reactive towards alkali metal amides than 3-nitropyridine.

Arylamination of heterocyclic quinones has been shown to proceed similarly to their alkylamination (see Schemes 17 and 18) [68–70, 93].

4 Amination of Azoles

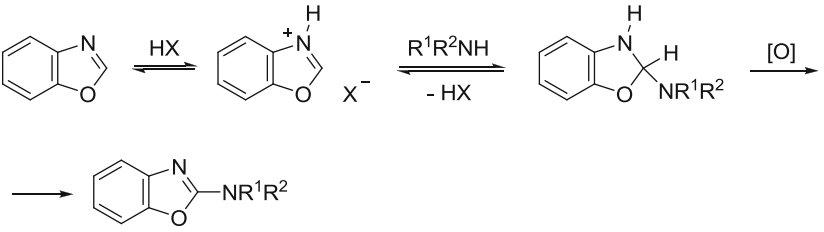
Unlike π-deficient azines and π-excessive heterocycles with the only pyrrole-like heteroatom, a number of azoles can be attributed to π-amphoteric systems. Indeed, it happens that a number of ring carbon atoms in an azole ring may carry partial positive charges, while others are negatively charged. Depending on values of these charges, each azole system demonstrates either π-deficient or π-excessive nature. For instance, non-condensed pyrazoles and imidazoles undergo electrophilic substitution reactions nearly exclusively, while benzimidazoles react with both electrophiles and nucleophiles. In regard to the classical Chichibabin reaction (thermal and non-oxidative) all azoles can be divided into three groups [9, 10, 15]. The first one includes non-condensed imidazoles, pyrazoles, 1,2,3-triazoles, and some other systems, which do not react with sodium amide. The second relatively small group inolves benzimidazoles, naphthoimidazoles, and their condensed analogues, which are readily aminated at the μ-carbon atom. The third group consists of low basic azoles, like benzoxazole or benzothiazole, which are destroyed by action of metal amides. To the best of our knowledge, no reports on oxidative amination of the first and the second groups of compounds have so far been published. However, a significant progress has recently been achieved in the field of amination of low basic azoles, representing the third group.

The amination strategy suggested for benzoxazoles and benzothiazoles consists in their activation by Brønsted or Lewis acid [94]. Such protonation (coordination) of benzazoles facilitates the formation of σ^H-adducts, which are then oxidized to produce the corresponding 2-aminoazole (Scheme 39).

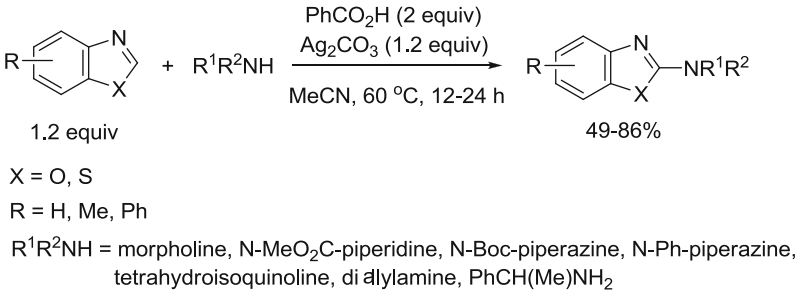
Indeed, benzoxazoles and benzothiazoles react smoothly with secondary and primary aliphatic amines in acetonitrile in the presence of benzoic acid and silver carbonate, thus giving rise to the corresponding 2-amino derivatives (Scheme 40) [94]. Also the reaction of 6-methylbenzothiazole with morpholine has been carried out in the presence of $Zn(OAc)_2$ as the Lewis acid (catalyst) and Ag_2O as oxidant.

Amination of these substrates can also be achieved in good yields (up to 91%) with formamides [94]. It has been suggested that formamides undergo acid-promoted decarbonylation under the reaction conditions, which are more drastic (130°C, 12 h) than used normally, thus affording the corresponding amines.

Catalytic amounts of $Co(OAc)_2$ or $Mn(OAc)_2$ in combination with *tert*-butyl hydrogen peroxide (1.2 equiv.) as oxidant proved to be effective for amination of benzoxazoles, benzothiazoles, and 2-phenyl-1,3,4-oxadiazole [95]. It is worth noting that in amination of benzoxazoles with secondary aliphatic amines the cobalt catalyst provides better results, while the manganese catalyst is more effective for a similar reaction with primary alkylamines and ammonia. Also the reactions of benzoxazoles with secondary aliphatic amines or formamides have been performed successfully with $Cu(OAc)_2$ (20 mol.%) and oxygen as oxidant [96]. Other azoles do not react with primary alkylamines in the presence of this oxidant. In contrast, when $FeCl_3$ was used in 0.25–1 equiv. amounts, amination of benzoxazoles and 2-aryl-1,3,4-oxadiazoles (with the exception of their nitro derivatives) proved to



Scheme 39 Acid-promoted oxidative amination of benzoxazole



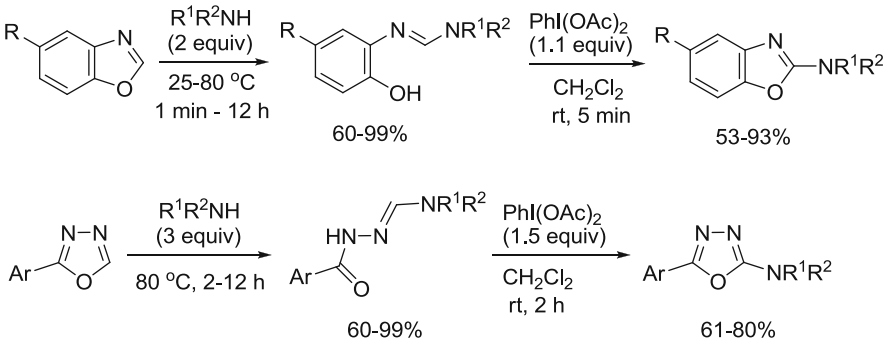
Scheme 40 Acid-promoted oxidative amination of benzoxazoles and benzothiazoles

occur by action of both primary and secondary aliphatic amines or formamides [97].

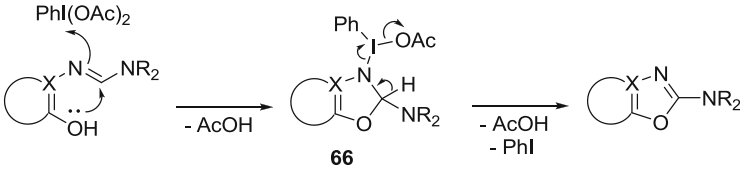
A metal-free protocol for amination of azoles has recently been reported [98]. It includes two steps: (1) the ring opening of benzoxazoles or oxadiazoles on heating with secondary aliphatic amines and (2) oxidative ring closure of the resulting amidines on their treatment with (diacetoxyiodo)benzene as oxidant within a short time at room temperature (Scheme 41). The same process can also be performed as a one-pot synthesis without isolation of the amidine intermediate.

It has been found that this oxidative cyclization does not exhibit kinetic isotope effect ($k_H/k_D = 1.0$), thus indicating that the cleavage of the μ-C–H bond in the amidine adduct is not involved into the rate-determining step. Although the exact mechanistic details are not clear yet, it is assumed that the I^{III} species are initially coordinated with the amidine nitrogen atom, followed by ring closure and elimination of iodobenzene and acetic acid from the azoline intermediate **66** (Scheme 42). It is worth mentioning that the reaction proceeds under mild conditions and is free from acid or metal catalyst.

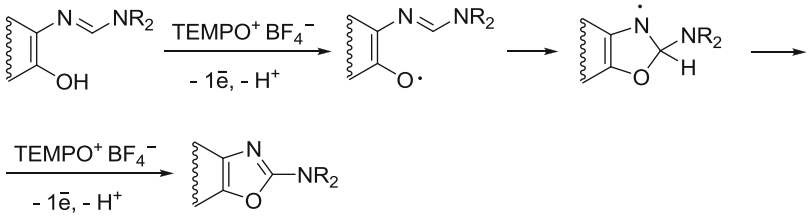
Amination of benzoxazoles and 1,3,4-oxadiazoles with secondary amines in the presence of Brønsted or Lewis acid and 2,2,6,6-tetramethylpiperidine-*N*-oxoammonium tetrafluoroborate ($TEMPO^+BF_4^-$) as oxidant has also been reported [99]. The reaction is supposed to proceed via the acyclic amidine intermediate, which is converted into the corresponding 2-aminoazole through stepwise



Scheme 41 Metal-free two-step amination of benzoxazoles and 1,3,4-oxadiazoles



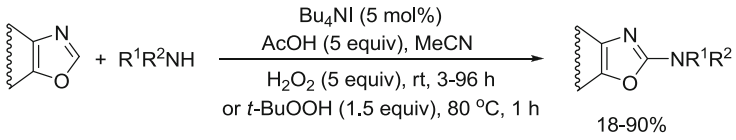
Scheme 42 Proposed mechanism for the ring closure step of the metal-free amination reaction



Scheme 43 Proposed mechanism for the ring closure step at the amination of azoles with $TEMPO^+BF_4^-$ as oxidant

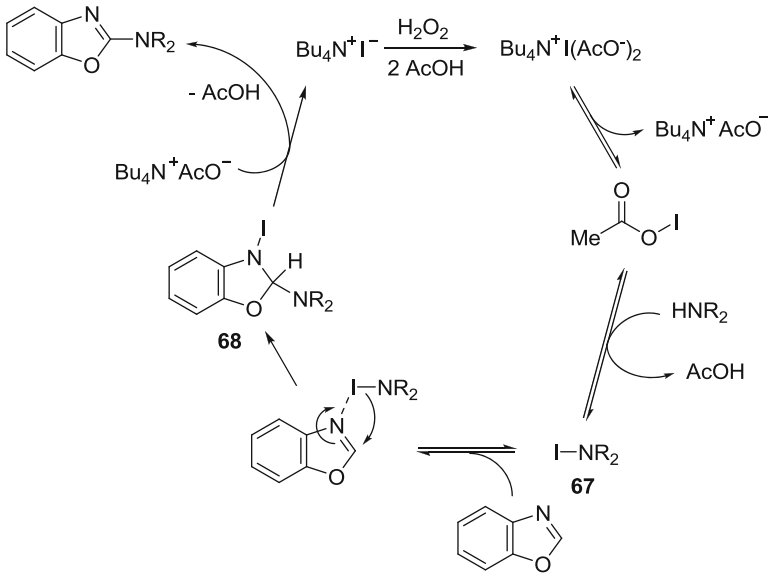
single-electron transfer mechanism (Scheme 43). It has been shown that conversion of amidines into aminoazoles can also be achieved with DDQ as oxidant.

Benzoxazoles (5-H, 5-Me, 5-Cl, 5-*t*-Bu, 6-Me, 6-NO_2) and naphtho[2,1-*d*] oxazole were aminated with alkylamines in acetonitrile in the presence of catalytic amounts of tetrabutylammonium iodide, aqueous solution of H_2O_2 or *t*-BuOOH and acetic acid (Scheme 44) [100, 101]. The reaction occurs quite well even with aqueous ammonia, although the catalyst quantity must be increased from 5 to



R^1R^2NH = pyrrolidine, morpholine, piperidine, N-Me-piperazine, diallylamine, $(PhCH_2)_2NH$, *i*-Bu_2NH, Et_2NH, $BuNH_2$, *t*-$BuNH_2$, $PhCH_2NH_2$, *cyclo*-C_5H_9 *etc.*

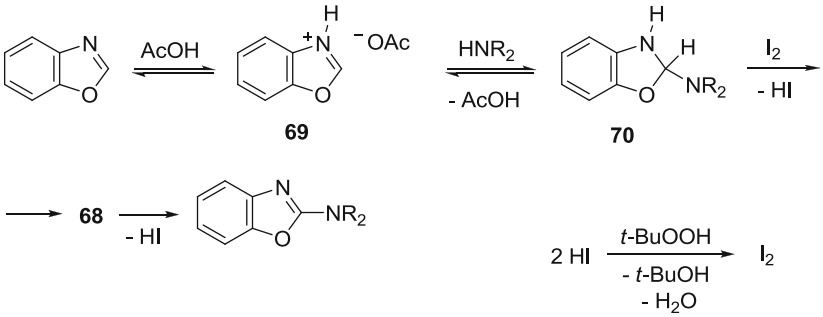
Scheme 44 Iodide-catalyzed oxidative amination of fused oxazoles



Scheme 45 Proposed mechanism for iodide-catalyzed amination of benzoxazoles

10 mol%. Benzothiazole and *N*-methylbenzimidazole did not enter this transformation.

Addition of the radical scavenger TEMPO proved to show a negligible impact on the reaction, thus indicating that the radical mechanism has to be ruled out. Besides that, the in situ generation of I_2 and its subsequent participation as a mild Lewis acid could also be excluded, since the addition of catalytic amount of I_2 (without co-oxidant) did not result in the formation of amino product. At the same time, the use of stoichiometric quantity of ICl (a potent source for the formation of iodonium ions IR_2^+) led to 2-(morpholin-4-yl)benzoxazole in 65% yield. Based on these observations, the mechanism involving the formation of I^+ and *N*-iodoamines **67** has been advanced (Scheme 45). Indeed, the addition of authentic compounds **67** to the starting benzoxazole gave 2-amino-3-iodobenzoxazolines **68** which were converted into the corresponding 2-aminobenzoxazoles after base-induced elimination of HI.

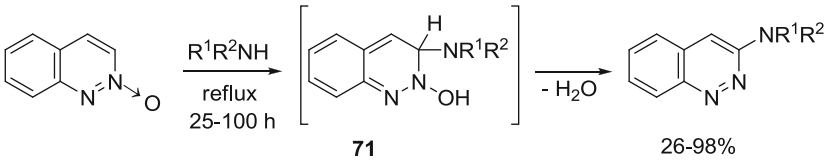


Scheme 46 Proposed mechanism for iodine-catalyzed amination of benzoxazoles

Benzoxazoles have also been aminated with secondary or primary aliphatic amines (1 equiv.) in the presence of catalytic amount of iodine (5 mol%), aqueous *t*-butyl hydroperoxide (1 equiv.), and acetic acid (1.1 equiv.) at ambient temperature for 12 h [102]. Authors believe that protonation of benzoxazole results in the formation of equilibrium amount of the salt **69**, which adds alkylamine to form 2-aminobenoxazoline **70** (Scheme 46). Interaction of **70** with iodine generates 2-amino-3-iodobenzoxazoline **68**, which eliminates HI to give the amination product. The reaction cycle is maintained due to oxidation of iodide ions with *t*-BuOOH. It is important to note that this environmentally benign method produces tertiary butanol and water as by-products. Use of *N*-iodosuccinimide catalyst in combination with aqueous hydrogen peroxide in acetonitrile solution allows to reduce the reaction time to 4 h [103]. Benzothiazole under the same conditions remaines unchanged.

5 Amination via the *cine*- and *tele*-Substitution

There are numerous examples of σ^H-adduct transformations proceeding via departure of an anionic leaving group from a ring position different from that to which a nucleophilic reagent has been added. When leaving group departs from a position which is vicinal to the addition site, the *cine*-substitution takes place (for definition, see IUPAC Gold Book: goldbook.iupac.org). When a leaving group departs from a more remote position of the ring or from a side chain, such processes are called *tele*-substitutions. For review on *cine*- and *tele*-substitution reactions of electron-deficient arenes see [104].



Scheme 47 *cine*-Amination of cinnoline 2-oxide

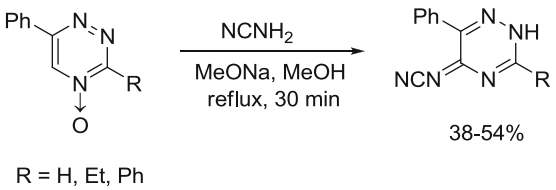
5.1 cine-*Amination*

A typical example of the *cine*-amination is interaction of cinnoline-2-oxide with an excess of primary or secondary amines, producing 3-aminocinnolines in 26–98% yields (Scheme 47) [105]. The lowest yield corresponds to the most bulky isopropylamine. It is evident that the reaction proceeds via the intermediate adduct **71** followed by its aromatization with elimination of water. Interestingly, the reaction of cinnoline-2-oxide with propylamine or pyrrolidine, which takes place in the presence of $AgPy_2MnO_4$, also affords the corresponding 3-aminocinnolines as the only products in 60 and 95% yields, respectively. Thus, even under oxidative conditions the *cine*-substitution pathway prevails on the oxidative amination. At the same time, as it has been already mentioned in Sect. 3.2 (Scheme 29), pyrimidopyridazine *N*(2)-oxide **46** is aminated in the presence of $AgPy_2MnO_4$ both with loss of the N-oxide function and with its retention.

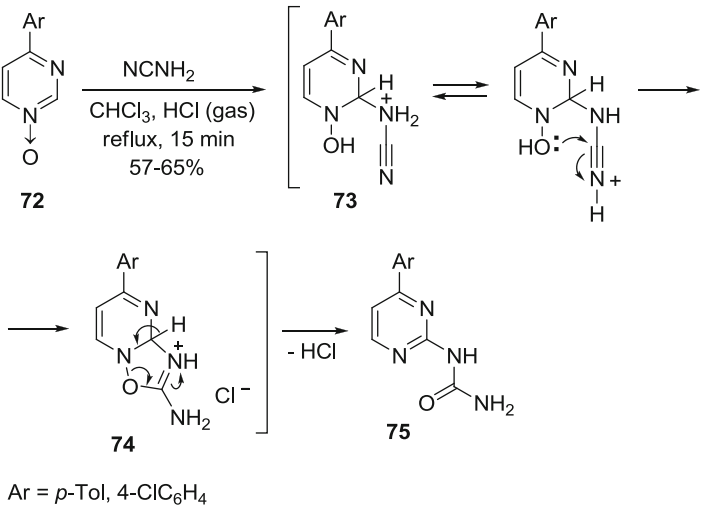
When treated with cyanamide in the presence of sodium methoxide 1,2,4-triazine 4-oxides are transformed into 5-cyanamino-1,2,4-triazines (Scheme 48) [106]. Presumably, these basic conditions are favorable for generation of more active nucleophilic species (via the equilibrium formation of $NCNH^-$ anions), and also they facilitate aromatization of σ^H-adducts via the E1cb elimination of water.

Pyrimidine 1-oxides **72**, which are less electrophilic than triazines, do not react with cyanamide in the presence of a base. However, treatment of **72** with cyanamide under acidic conditions (dry HCl) results in the formation of 4-aryl-2-ureidopyrimidines **75** (Scheme 49) [107]. It is evident that in situ protonation of these N-oxides significantly enhances their ability to give σ^H-adducts **73**. It triggers the subsequent cyclization and the ring opening process (**73**→**74**→**75**), thus resulting in the formation of **75**. Hydrolysis of the latter on reflux in formic acid provides the corresponding 2-aminoperimidines.

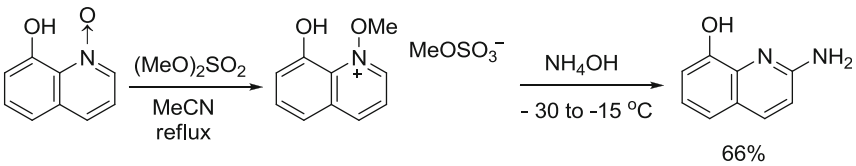
The presence of the N-oxide group in heterocyclic substrate opens another way for *auto*-aromatization of the σ^H-adducts. This is achieved via preliminary *O*-alkylation or *O*-acylation of the N-oxide group followed by addition of a nucleophile. Aromatization of the σ^H-adducts in these cases is based on elimination of the corresponding alcohol or carboxylic acid. The *O*-alkyl and *O*-acyl derivatives are usually not isolated, but it happens quite often that they are formed in situ during the reaction course. For instance, 2-amino-8-hydroxyquinoline has been obtained in



Scheme 48 *cine*-Amination of 1,2,4-triazine 4-oxides



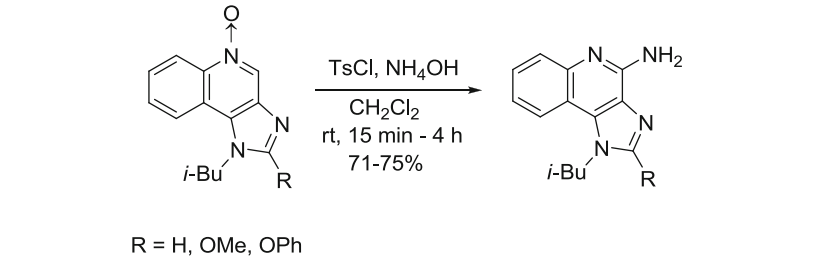
Scheme 49 Acid-catalyzed transformation of 4-arylpyrimidine-1-oxides by action of cyanamide



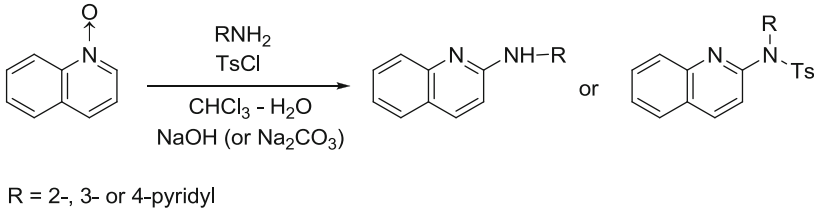
Scheme 50 *cine*-Amination of *N*-methoxy-8-hydroxyquinolinium salt

a two-step one-pot procedure including *O*-methylation followed by quenching of the reaction mixture with aqueous ammonia at low temperature (Scheme 50) [108].

1-Isobutyl-2-R-1*H*-imidazo[4,5-*c*]quinoline 5-oxides were converted into the corresponding 4-amino derivatives by reacting with concentrated ammonium hydroxide and tosyl chloride in dichloromethane (Scheme 51) [109]. Use of aqueous or methanolic ammonia in the reaction with quinoline 1-oxides led to the formation of 2-aminoquinolines along with 2-quinolones or 2-methoxyquinolines, as by-products [110]. A better selectivity in this amination reaction has been achieved on using Et_3N/NH_4Cl buffer system.



Scheme 51 Amination of 1*H*-imidazo[4,5-*c*]quinoline 5-oxides in the presence of acylating agent

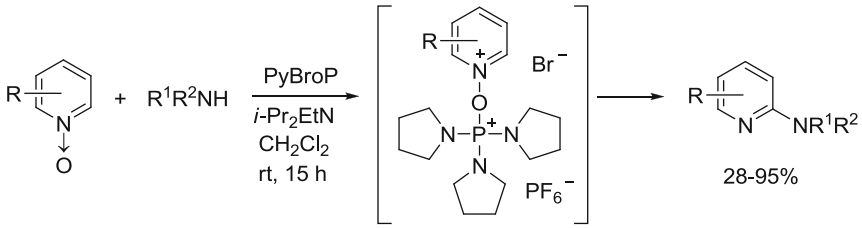


Scheme 52 *cine*-Amination of quinoline 1-oxide with aminopyridines

When quinoline 1-oxide was treated with 2-aminopyridine in the presence of tosyl chloride under phase-transfer conditions in alkaline medium *N*-(pyridin-2-yl) quinolin-2-amine was obtained in 80% yield (Scheme 52) [111]. Also 3- or 4-aminopyridines can be regarded as nucleophiles, and their use in the same reaction with quinoline 1-oxide has been shown to afford *N*-tosyl derivatives of the corresponding *N*-arylquinolin-2-amines in 15 and 53% yields, respectively. It is worth noting that the reactions of quinoline 1-oxide with *N*-tosyl derivatives of 2-, 3-, or 4-aminopyridine gave the corresponding 2-(*N*-tosyl-*N*-arylamino)quinolines in considerably higher yields.

In contrast to quinoline N-oxides, the amination of pyridine N-oxides with NH_4OH/TsCl or 2-aminopyridine/TsCl was unsuccessful due to a variety of side reactions: nucleophilic addition at position 4, dimerization, tosylation of the amination product, and nucleophile itself [111].

It has recently been demonstrated that bromo-*tris*-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) can be functioning as a mild activator of azine N-oxide providing regioselective addition of *N*-nucleophiles (amines, sulfonamides, and NH-heterocyclic compounds) to pyridine, quinoline, and isoquinoline N-oxides (Scheme 53) [112, 113]. A strong regiochemical preference for the *ortho*-substitution pattern in all these cases is likely caused by specific electrostatic attraction of nucleophilic species and the intermediate phosphonium salt **76**. This synthetic procedure was successfully extended for other types of nucleophilic reagents (phenols, thiols, malonates).

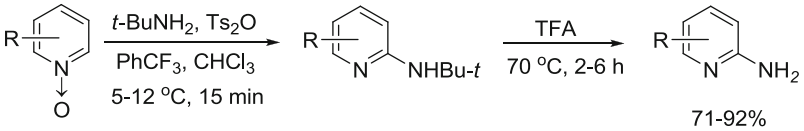


76

R = H, 4-CO_2Me,2-Me, 3-Me, 4-CN, 4-OMe

R^1R^2NH = NH_3, $MeNH_2$, $PrNH_2$, *t*-$BuNH_2$, *cyclo*-$C_6H_{11}NH_2$, $PhCH_2NH_2$, allylamine, pyrrolidine, $MeS(O)_2NHMe$ $PhS(O)_2NHMe$, $PhS(O)_2NHPh$, imidazole, pyrazole, benzimidazole, 2- and 4-pyridones, 4-pyrimidone, 3-isoquinolone *etc.*

Scheme 53 Use of PyBroP as a mild activator of pyridine N-oxides



R = H, 3-Me, 4-Me, 4-Ph, 4-Cl, 4-MeO, 2-CO_2Me, 4-CO_2Me, pyridin-2-yl

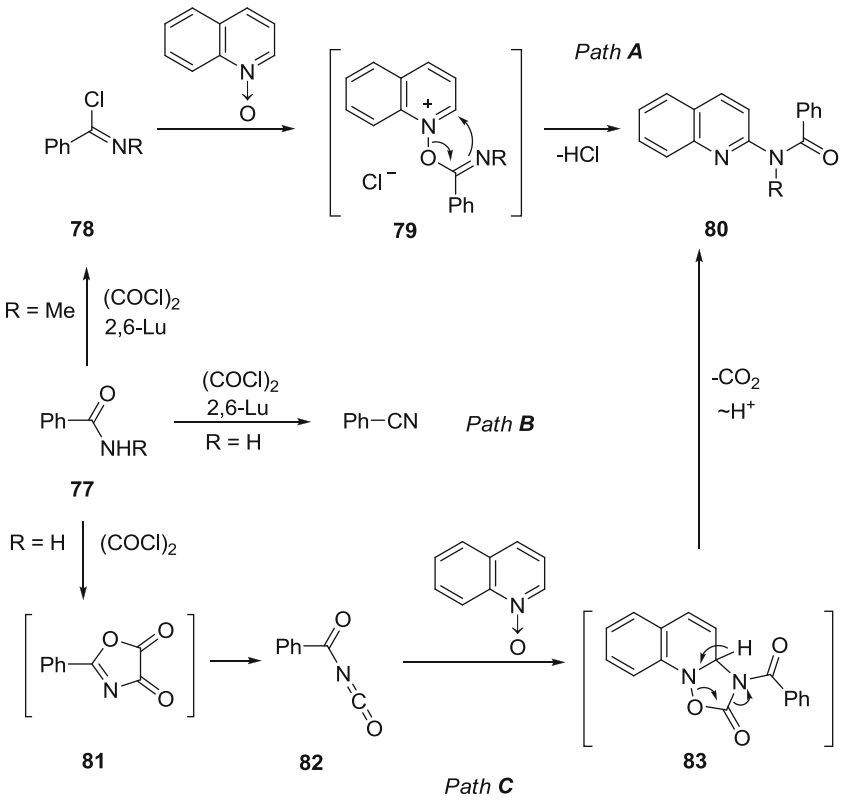
Scheme 54 Synthesis of 2-aminopyridines via *cine*-substitution reaction

Unfortunately, due to a relatively high cost and instability of the phosphonium reagent, the abovementioned approach appears to be not suitable for large-scale syntheses.

Use of *t*-$BuNH_2$ and Ts_2O allowed to convert pyridine N-oxides into 2-(*t*-butylamino)pyridines in high yields and high 2/4-regioselectivity (>50/1) (Scheme 54) [114]. Treatment of a crude reaction mixture with TFA provides effective removal of the *t*-butyl group. The same one-pot procedure is suitable for the synthesis of 2-aminoquinolines and 1-aminoisoquinolines from the corresponding N-oxides.

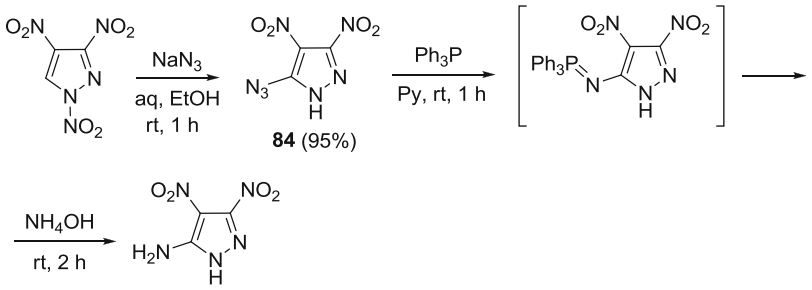
Saccharin, phthalimide, *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide, diethyl-*N*-(*tert*-butoxycarbonyl)phosphoramidate, and HMDS have recently been screened as ammonia surrogates in the amination of 3,5-disubstituted pyridine N-oxides activated by TsCl (*i*-Pr_2NEt, CH_2Cl_2, 0°C) [115]. Relatively cheap and readily available saccharin is an ideal reagent for this amination, providing a good conversion and a high 2/6-regioselectivety. Also it is important that cleavage of saccharin intermediates can be achieved in a one-pot fashion on treatment with aq. HCl or H_2SO_4.

In 1969 Abramovich reported the formation of 2-amidoquinolines **80** from quinoline N-oxides on their treatment with imidoyl chlorides **78** (Scheme 55, *Path **A***) [116].



Scheme 55 Proposed mechanisms for the formation of 2-amidoquinolines **80** from quinoline N-oxide and carboxamides

This method was later simplified by means of in situ generation of imidoyl chlorides from the secondary carboxamides, oxalyl chloride, and 2,6-lutidine (2,6-Lu) in the presence of heterocyclic N-oxides [117]. Unfortunately, this procedure cannot be applied to primary amides, since chloroimidates are prone to eliminate hydrogen chloride, thus giving the corresponding nitriles (Scheme 55, *Path **B***). However, the problem was solved by using primary amides with oxalyl chloride without 2,6-lutidine [118]. It has been shown by NMR that in this case the process does not involve the intermediacy of imidoyl chloride **78**. Instead, unstable oxazoline-4,5-dione **81** is initially formed which is then converted into benzoyl isocyanate **82** (Scheme 55, *Path **C***). The latter undergoes 1,3-dipolar cycloaddition with quinoline N-oxide followed by decarboxylative aromatization of **83** into 2-benzamidoquinoline **80**. Besides quinoline N-oxides, isoquinoline- and benzo[*c*] quinoline N-oxides were used in this reaction as substrates, while acetamide and various aromatic carboxamides proved to be appropriate nucleophiles. Yields of the target amides were in the range 62–99%.



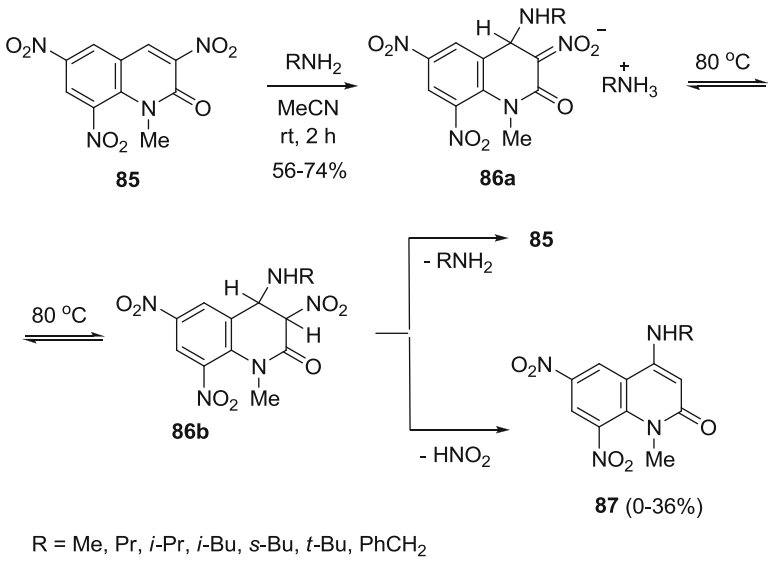
Scheme 56 Synthesis of 5-amino-3,4-dinitropyrazole

The deoxygenative methodology allows incorporating azole residues into azaaromatic scaffolds. Pyridine, quinoline, isoquinoline, azaindole, and pyrimidine N-oxides were converted to their α-triazole and α-diazole derivatives by treatment with the corresponding *p*-toluenesulfonylazoles and Hunig's base at elevated temperatures [119] or by treatment with sulfuryldiimidazole in nonpolar solvents at elevated temperatures [120].

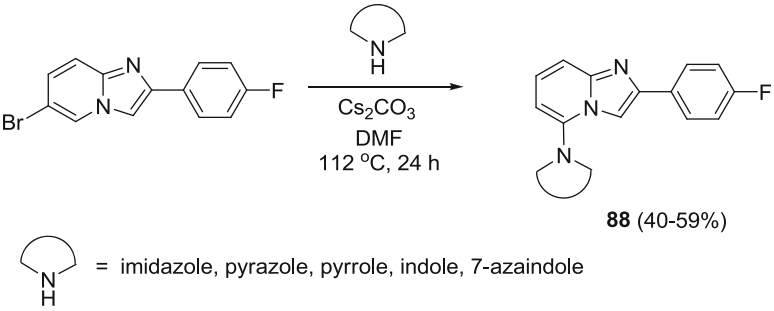
The *cine*-substitution reactions in *N*-fluoropyridinium salts with various nucleophiles, including *N*-nucleophiles, have been reviewed [121]. However, this approach did not find practical applications because of low yields of 2-substituted pyridines and the formation of complex mixtures of reaction products.

Azoles bearing a nucleofugal group attached to the pyrrole-type nitrogen atom can undergo *cine*-substitution. Such reactions are known to occur in the series of 1,4-dinitropyrazoles, 1,4-dinitroimidazoles, 1-nitro-1,2,4-triazoles, and 2,*n*-dinitroindazoles [104]. Ammonia, primary and secondary amines as well as NH-heterocycles were used as nucleophiles in these reactions. Usually, an entering group occupies the 5-position of an azole ring. Recently, it was found that *cine*-substitution of the *N*-nitro group in 1,3,4-trinitropyrazole proceeds under milder conditions than in 1,4-dinitropyrazoles and produces 5-substituted 3,4-dinitropyrazoles, e.g., **84**, in high yield (Scheme 56) [122]. The reaction of 1,3,4-trinitropyrazole with ammonia in various solvents at temperatures from −30 to +20°C gave only decomposition products. However, 5-amino-3,4-dinitropyrazole was obtained in 78% yield by reacting 5-azido derivative **84** with triphenylphosphine in pyridine followed by treatment with concentrated aqueous ammonia.

In some cases, the *cine*-aminodenitration does occur with elimination of the *C*-nitro group. Thus, 1-methyl-3,6,8-trinitroquinolone **85** readily reacts with primary alkylamines to give adducts **86** in the form of alkylammonium salts **86a** (Scheme 57) [123, 124]. The latter are converted on heating into 4-alkylamino derivatives **87** in low to moderate yields together with recovery of a large amount of the starting 1-methyl-3,6,8-trinitroquinolone. This result can be explained by two ways for the transformation of adducts **86b** with elimination of nitrous acid or alkylamine, as shown in Scheme 57.

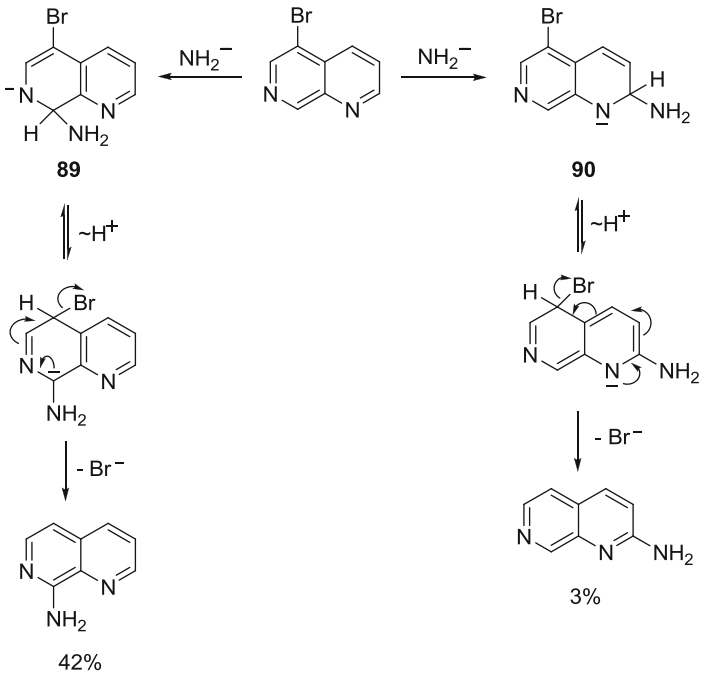


Scheme 57 *cine*-Amination of 1-methyl-3,6,8-trinitroquinolone



Scheme 58 *cine*-Substitution in 6-bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine by action of NH-azoles

cine-Amination is very typical for heteroaromatic halides. Indeed, 5-bromopyrimidines, 7-bromo-5-azaquinoxaline, 5-chloro- and 5-bromopyridazine-3,6-diones, 2-bromothiophene, and 5-chloro- and 5-bromo-1-methylimidazoles have been shown to undergo *cine*-amination on treatment with secondary aliphatic amines, their carboxamides, or KNH_2/NH_3 [104]. It has also been found that 6-bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine reacts with NH-heterocycles in the presence of Cs_2CO_3 in DMF to produce the corresponding 5-hetaryl derivatives **88** in reasonable yields (Scheme 58) [125].



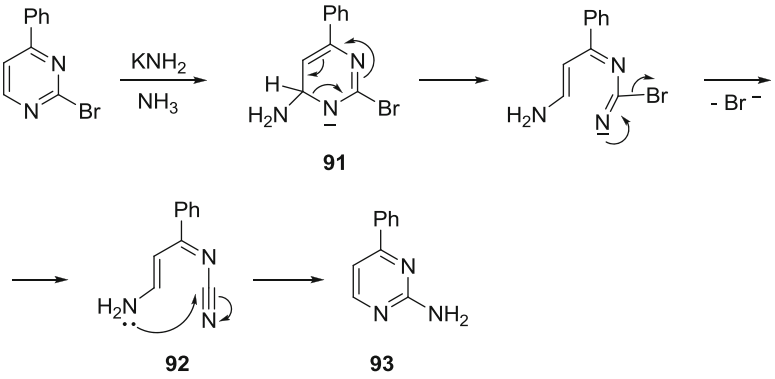
Scheme 59 An example of *tele*-amination reactions

5.2 tele-*Amination*

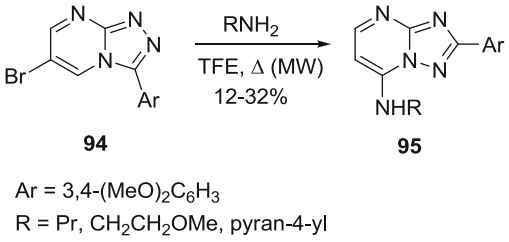
A good illustration of the *tele*-amination reactions is interaction of 5-bromo-1,7-naphthyridine with KNH_2 in liquid ammonia, leading to a mixture of 8-amino- and 2-amino-1,7-naphthyridines in 42 and 3% yields, respectively (Scheme 59) [126]. During the reaction the amide ion attacks C-2 and C-8 atoms, which are activated by the adjacent aza groups. The intermediate σ^H-adducts **89** and **90** are then stabilized by the loss of hydrogen bromide. Two excellent reviews on the *tele*-substitution reactions were published in 2001 and 2011 [104, 127].

5.3 *Amination via the ANRORC Mechanism*

There are *cine*- and *tele*-amination reactions which proceed via a special multi-step pathway, known as the ANRORC mechanism (***A***ddition of a ***N***ucleophile, ***R***ing ***O***pening, ***R***ing ***C***losure) (for reviews on this topics, see [11, 23, 128]). For instance, 2-bromo-4-phenylpyrimidine reacts with KNH_2 in liquid ammonia to afford 2-amino derivative **93** (Scheme 60). Thorough investigation of this reaction has shown that it proceeds via the formation of σ^H-adduct **91** followed by opening of the



Scheme 60 The ANRORC amination of 2-bromo-4-phenylpyrimidine



Scheme 61 Interaction of 6-bromo-[1,2,4]triazolo[4,3-*a*]pyrimidine **94** with alkylamines

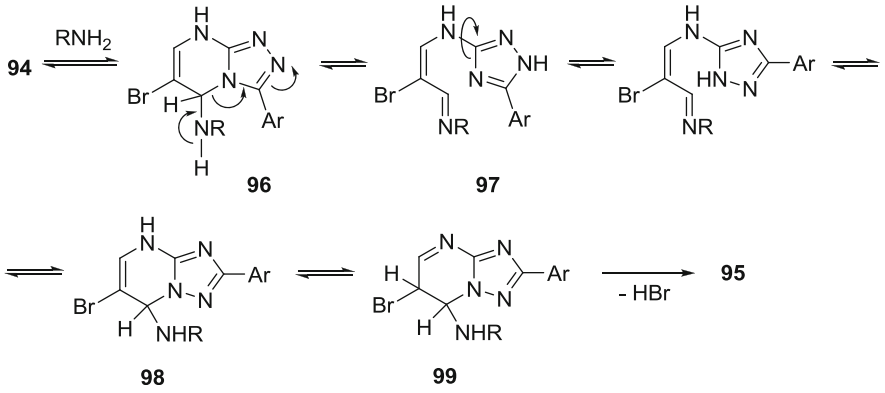
pyrimidine ring and elimination of the bromide ion. Then the open-chain intermediate **92** undergoes cyclization into aminopyrimidine **93**.

It has recently been found that the ANRORC mechanism is realized in the reaction of 6-bromo-[1, 2, 4]triazolo[4,3-*a*]pyrimidine **94** with aliphatic amines under microwave irradiation, thus affording *N*-alkyl-[1,2,4]triazolo[1,5-*a*] pyrimidin-7-amines **95** (Scheme 61) [129].

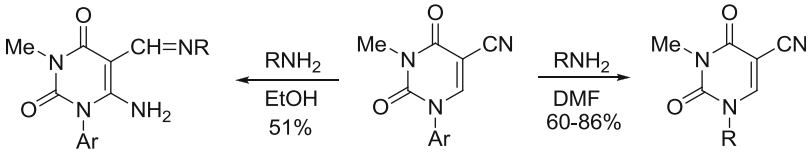
This transformation starts with the addition of amine to C-5 of **94** resulting in the formation of the σ^H-adduct **96** (Scheme 62). Subsequent opening of the pyrimidine ring, rotation around C(4)-N(exo) in the intermediate **97**, recyclization with participation of the triazole ring (**97**→**98**→**99**), and elimination of HBr comprise the set of steps to form the final product **95**.

Treatment of 5-cyanouracil **100** with 1-aminopropane-2-ol in anhydrous ethanol gave 6-aminouracil **101** [R = $CH_2CH(OH)Me$] in 51% yield (Scheme 63) [130]. However, when ethanol was replaced with anhydrous DMF the course of the reaction was changed and compounds **102** were obtained in good yields.

It has been suggested that both types of compounds, **101** and **102**, are originating from the ANRORC reactions through intermediacy of the common open-chain intermediate **103**. In protic solvents the acid-catalyzed cyclization appears to occur, thus leading to the Dimroth rearrangement product **101** (Scheme 64, *Path A*). In aprotic DMF the alkylamino group of **103** is active enough for the



Scheme 62 Proposed mechanism for the transformation **94**→**95**



Ar = 4-NO_2-C_6H_4

R = $CH_2CH(OH)Me$, $CH_2CH(OH)CH_2OH$, $CH(CH_2OH)_2$ *etc.*

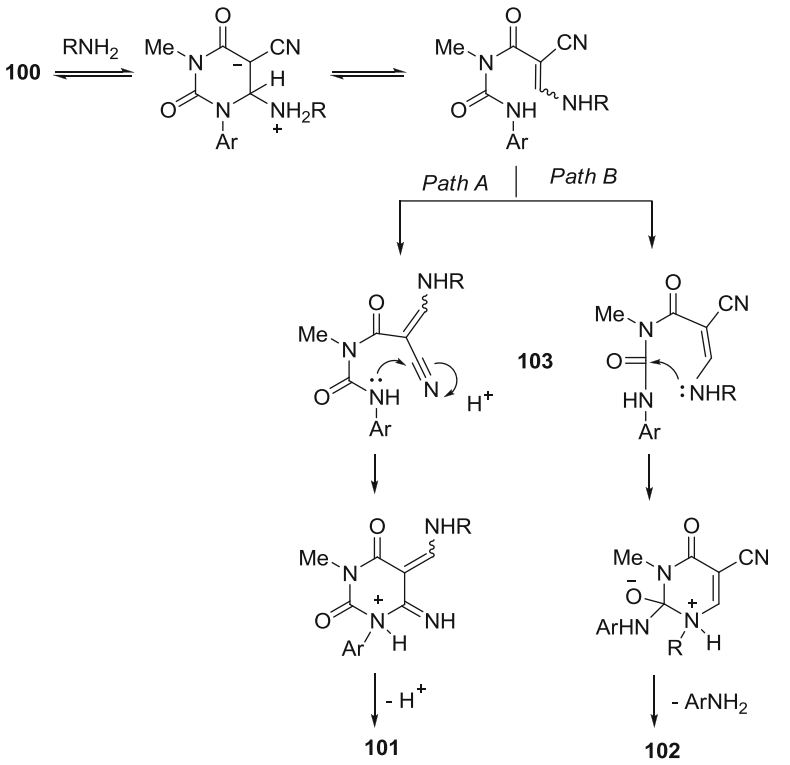
Scheme 63 Reactions of 5-cyanouracil **100** with alkylamines

intramolecular addition to the carboxamide moiety to give the cyanide derivative **102** (Scheme 64, *Path B*). For review on recent advances in the Dimroth rearrangement, see [131].

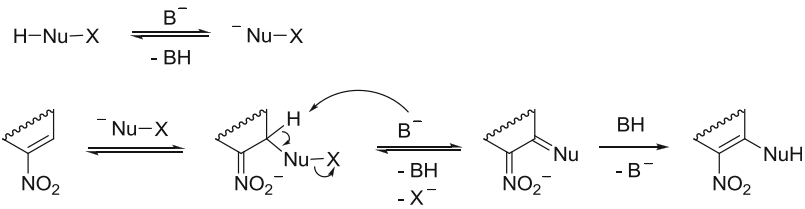
Also it should be noted that a very specific kind of the ANRORC transformations have been mentioned in the previous section, when discussing oxidative amination of benzoxazoles and 1,3,4-oxadiazoles (Sect. 4, Schemes 41 and 42).

6 Amination via the Vicarious Nucleophilic Substitution of Hydrogen

The VNS of hydrogen consists of the addition of a nucleophile bearing a leaving group X attached to the nucleophilic center to an electrophilic aromatic substrate followed by base-induced β-elimination of HX from the initially formed σ^H-adduct, as shown in Scheme 65.



Scheme 64 ANRORC transformations of 5-cyanouracil **100**



Scheme 65 Schematic representation of the VNS reaction

The theory and practice of the VNS reactions have been examined in detail by the group of Prof. M. Mąkosza (for reviews, see [14, 18, 20–22, 25, 36, 37]. This well-developed methodology has been extended to many organic reactions, such as direct introduction of alkyl, hydroxy, and amino substituents into electron-deficient arenes (mainly nitroarenes), azines, and nitro derivatives of heteroaromatic compounds. Several excellent reviews dedicated specially to the VNS reactions of heterocyclic compounds have been published [18, 132].

To perform the VNS amination, reagents of the general formula NH_2X (hydroxylamine, *O*-methylhydroxylamine, 4*H*-1,2,4-triazol-4-amine, 1,1,1-trimethylhydrazonium iodide, sulfenamides) are used. The vicarious leaving group X (OH, OMe, NMe_3, triazolyl, RC(S)S) is needed first to facilitate deprotonation of the aminating agent and to provide some stabilization of the corresponding *N*-anion. Besides that, it serves as a good leaving group in the base-induced elimination of HX.

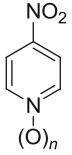
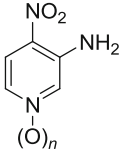
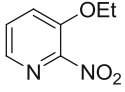
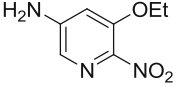
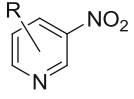
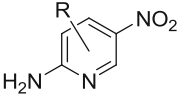
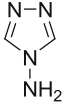
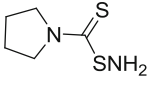
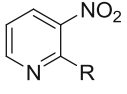
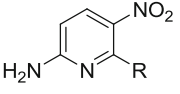
Recent examples of the VNS amination reactions in the series of six- and five-membered heterocycles and their benzo-fused analogues are summarized in Table 3. Nitro derivatives of pyridines, quinolines, isoquinolines, and quinoxalines proved to be especially suitable substrates. The reaction takes place in the *ortho*- or *para*-positions relative to the nitro group. Its exact orientation is governed by both the nature of substrate and substituents in the aromatic ring. For example, 3-nitropyridine is aminated at C-6 (*para* to the nitro group) exclusively, while 3-nitroquinoline and 4-nitroisoquinoline in the position 4 (*ortho* to the nitro group) and 1 (*para* to the nitro group), respectively. Although the reactions of 5- and 8-nitroquinolines produce a mixture of isomeric amino derivatives, amination at the *ortho*-position to the nitro group proved to be predominant one.

Examples of the VNS amination reactions for the series of five-membered heterocycles and their benzo-fused analogues are summarized in Table 4. In general, nitro derivatives of thiophene, pyrazole, imidazole, 2*H*-1,2,3-triazole, indole, benzimidazole, and porphyrin are less reactive than nitroazines. Indeed, mononitro substituted pyrazoles, imidazoles, and benzimidazoles bearing the NH moiety are not aminated under the VNS conditions at all. Most likely, this is due to deprotonation of NH-azoles under basic conditions, leading to the formation of the corresponding *N*-anions, which are inert to further nucleophilic attack. However, the presence of the second nitro group in azoles makes the latter enough reactive even in their anion forms. This may be exemplified by the successful amination of 3,5-dinitropyrazole [133]. The VNS amination reaction of 4-nitroimidazoles is often accompanied by their ring transformations [134, 135].

As for aminating agents, use of hydroxylamine provides a very simple and cheap procedure, while 1,1,1-trimethylhydrazonium iodide, 4*H*-1,2,4-triazol-4-amine, and *S*-(pyrrolidine-1-carbonothioyl)thiohydroxylamine usually afford better yields of the amination products. The feature of 4*H*-1,2,4-triazol-4-amine is that its application demands an inert atmosphere.

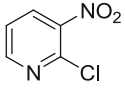
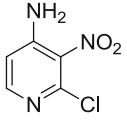
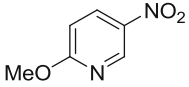
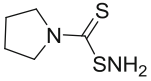
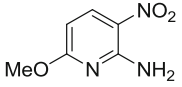
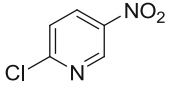
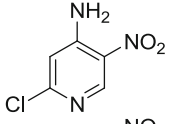
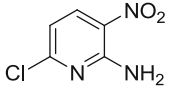
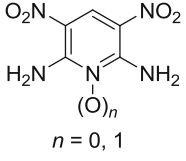
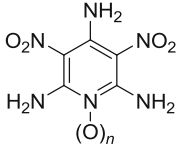
A rare example of the VNS-arylamination of 2-nitrothiophene by action of *N*,*S*-diphenylthiohydroxylamine as nucleophile has also been documented [136]. Unlike regioselective C(3)-amination of 2-nitrothiophene, the arylamination reaction affords a mixture of 3-phenylamino- and 5-phenylamino- derivatives in 1:3 ratio.

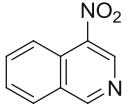
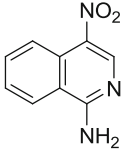
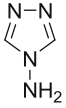
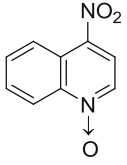
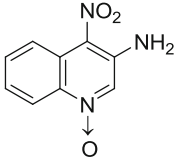
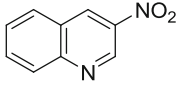
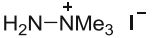
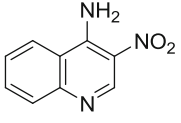
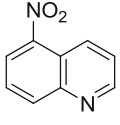
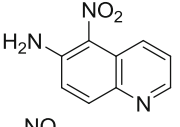
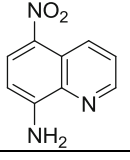
Table 3 Amination of six-membered heterocycles and their benzo-fused analogs via the vicarious nucleophilic substitution of hydrogen

Substrate	Aminating agent	Reaction conditions	Products	Yield (%)	References
 n = 0,1	NH_2OMe	$ZnCl_2$, t-BuOK, DMF, rt, 1–10 h		25–38	[137]
	NH_2OMe	$ZnCl_2$, t-BuOK, DMSO, rt, 1–10 h		7	[137]
 R = H, 4-Me, 4-Ph, 4-OEt, 4-CN, 4-CO_2Me, 4-CH=O (protected as the dioxolane), 4-Ac (protected as the dioxolane), 5-Me, 5-Ph	NH_2OH·HCl	$ZnCl_2$ (or without), KOH, EtOH, rt, 5 h		35–64	[138]
		t-BuOK, DMSO, N_2, rt, 5 h		11–79	
		t-BuOK, DMF, rt, 15 min		75 (R = 4-OEt)	[136]
 R = NH_2, OH	NH_2OMe	$ZnCl_2$, t-BuOK, DMSO (or DEM), rt, 1–10 h		58 (R = NH_2) 9 (R = OH)	[137]

(continued)

Table 3 (continued)

Substrate	Aminating agent	Reaction conditions	Products	Yield (%)	References
	NH_2OMe	$ZnCl_2$, *t*-BuOK, DME, rt, 1–10 h		34	[137]
		*t*-BuOK, DMF, rt, 15 min		42	[136]
	NH_2OMe	$ZnCl_2$, *t*-BuOK, DMSO, rt, 1–10 h		87	[137]
	NH_2OMe	$ZnCl_2$, *t*-BuOK, DEM, rt, 1–10 h		13	[137]
				9	
	$NH_2OH{\cdot}HCl$	KOH, H_2O, 0 °C, 1–5 h		39–40	[139]

	$NH_2OH{\cdot}HCl$	$ZnCl_2$ (or without), KOH, EtOH, rt, 5 h		23	[138]
		*t*-BuOK, DMSO, N_2, rt, 5 h		65	
	NH_2OMe	$ZnCl_2$, *t*-BuOK, DMF, rt, 1–10 h		21	[137]
		*t*-BuOK, DMSO, rt, 4 h		92	[140, 141]
		*t*-BuOK, DMSO, rt, 8 h		61	[140, 141]
				26	

(continued)

Table 3 (continued)

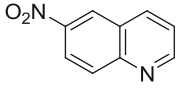
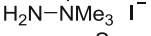
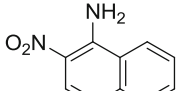
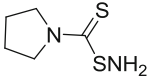
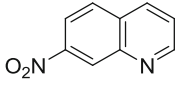
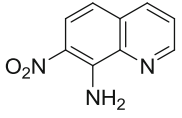
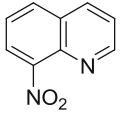
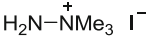
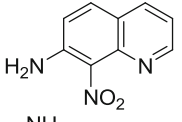
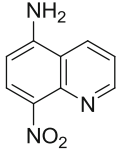
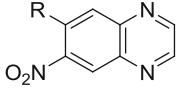
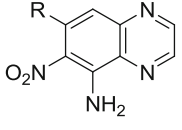
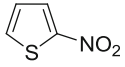
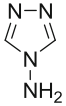
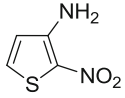
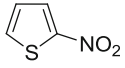
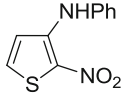
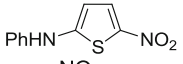
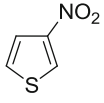
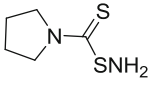
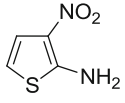
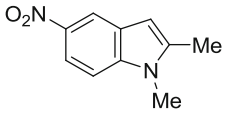
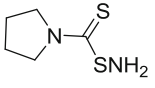
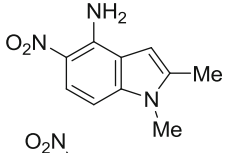
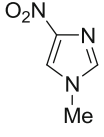
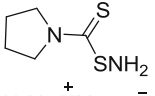
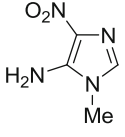
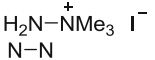
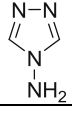
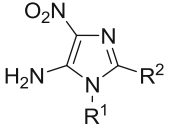
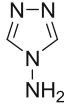
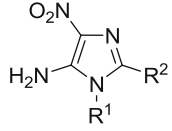
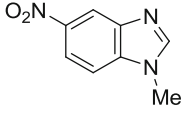
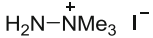
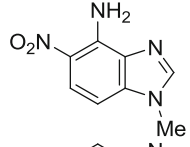
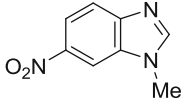
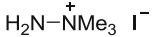
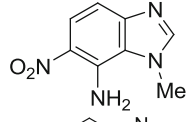
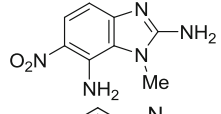
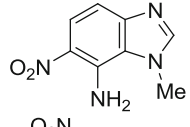
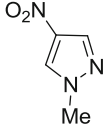
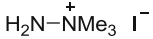
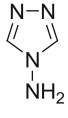
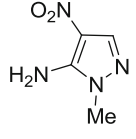
Substrate	Aminating agent	Reaction conditions	Products	Yield (%)	References
		*t*-BuOK, DMSO, rt, 1 h		95	[140, 141]
		*t*-BuOK, DMF, rt, 15 min		98	[136]
		*t*-BuOK, DMSO, rt, 2 h		92	[140, 141]
		*t*-BuOK, DMSO, rt, 4 h		68	[140, 141]
				18	
 R = H, F, Cl, Br	$NH_2OH{\cdot}HCl$	MeONa, MeOH, reflux, 1.5 h (or rt, 18 h)		27–56	[142]

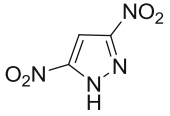
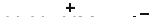
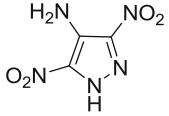
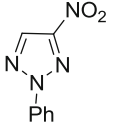
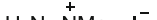
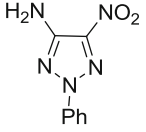
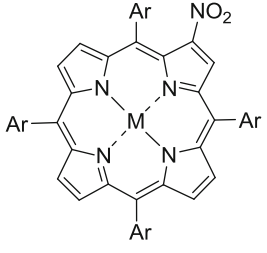
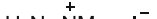
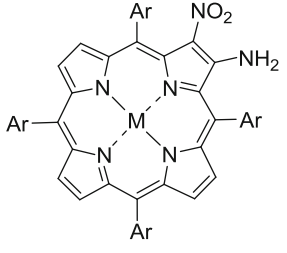
Table 4 Amination of five-membered heterocycles and their fused analogs via the vicarious nucleophilic substitution of hydrogen

Substrate	Aminating agent	Reaction conditions	Products	Yield (%)	References
		*t*-BuOK, DMSO, rt, 30 min		15	[143]
	PhSNHPh	*t*-BuOK, DMF, −25°C, 5 min		15	[136]
				42	
		*t*-BuOK, DMF, rt, 15 min		23	[136]
		*t*-BuOK, DMF, rt, 15 min		45	[136]
		*t*-BuOK, DMF, rt, 15 min		36	[136]
		*t*-BuOK (or MeONa), DMSO, rt, 20 h		56	[144]
		*t*-BuOK, DMSO, rt, 10 h		39	

(continued)

Table 4 (continued)

Substrate	Aminating agent	Reaction conditions	Products	Yield (%)	References
 R^1 = H, Me, CH_2Ph R^2 = Me, Ph, 4-$MeOC_6H_4$	 $NH_2OH{\cdot}HCl$	MeONa, DMSO, rt, 2 h KOH, MeOH, rt		30–72	[134, 135]
		*t*-BuOK, DMSO, rt, 10 h CuCl, *t*-BuOK, DMSO, rt, 10 h		39 81	[145]
		*t*-BuOK, DMSO, rt, 10 h	  	45 35	[145]
	 	*t*-BuOK, DMSO, rt, 40 h *t*-BuOK, DMSO, rt, 10 h		15–20 20	[146] [147]

		*t*-BuOK, DMSO, rt, 4 h		70	[133]
		*t*-BuOK, DMSO, rt, 10 h		93	[148]
 M = Zn, Cu Ar = Ph, 3-FC_6H_4, 3-ClC_6H_4, 3-MeC_6H_4, 3-$MeOC_6H_4$		KOH, DMSO, 70–80°C, 45 min–1.5 h, argon		64–89	[149]

7 Representative Procedures for the S_N^H-Amination

7.1 Synthesis of 1-Amino-4-Azafluorene by the Chichibabin Amination [43]

A mixture of 4-azafluorene (5 g, 30 mmol), $NaNH_2$ (4.68 g, 120 mmol), and *N*,*N*-dimethylaniline (100 mL) was placed into a three-necked flask equipped with a stirrer, thermometer, air condenser, and bubble counter. The mixture was heated for 5 h at 190–195°C (hydrogen evolution was noted). A black insoluble precipitate formed at the bottom of the flask. Dimethylaniline was decanted off and the precipitate was carefully decomposed by adding of 96% aqueous ethanol (50 mL) under cooling. Then, alumina (20 g) was added and ethanol was distilled off until dryness. The residue was placed onto a column (40 × 4 cm) packed with alumina and eluted with ethyl acetate to give 3.2 g (62%) of 1-amino-4-azafluorene as pale yellow crystals, mp 204–206°C (EtOH–EtOAc), R_f 0.52 (3:1 EtOAc–EtOH). IR (KBr), ν, cm^{-1}: 3,460, 3,300 (NH_2). UV, λ_{max} (log ε), nm: 212 (4.20), 249 (4.29), 270 (3.88), 285 (3.86), 301 (3.86). ^1H NMR (200 MHz, $CDCl_3$), δ, ppm: 3.65 (s, 2H, CH_2), 6.10 (br s, 2H, NH_2), 6.18 (d, $J = 5.5$ Hz, 1H, H-2), 7.05 (m, 1H, H-5), 7.30–7.40 (m, 2H, H-6 and H-7), 7.60 (m, 1H, H-8), 8.05 (d, $J = 5.5$ Hz, 1H, H-3). *m*/*z* (I, %): 182 (M^+, 100), 181 (29), 155 (6), 154 (6), 144 (7), 127 (7), 115 (9), 106 (9), 105 (29), 104 (18), 91 (30), 78 (31).

7.2 Oxidative Amination of 3-Phenyl-1,2,4,5-Tetrazine [49]

3-Phenyl-1,2,4,5-tetrazine (100 mg, 0.63 mmol) was dissolved in 10 mL of liq. NH_3 at −40 to −35°C; immediately the yellow color is observed. After 5 min, $KMnO_4$ (67 mg, 0.42 mmol = 1 redox equiv.) was added at once. After 10 min, EtOAc (25 mL) was added slowly. The ammonia is evaporated off, the solution is filtered through silica gel. The ethyl acetate is evaporated off in vacuo and the solid residue is crystallized from ether/pentane. 6-Phenyl-1,2,4,5-tetrazin-3-amine was obtained in 74% yield, mp 213.5–214.5°C. ^1H NMR (acetone-D_6), δ, ppm: 7.45 (br s, 2H, NH_2), 7.46–7.60 (m, 3H, Ph), 8.26–8.48 (m, 2H, Ph). *m*/*z* (I, %): 173 (M^+, 11), 103 (100), 42 (11).

7.3 Oxidative Amination of 1,3,7-Triazapyrene [55]

1,3,7-Triazapyrene (103 mg, 0.5 mmol) was dissolved at heating in dioxane (10 mL). Concentrated aqueous ammonia solution (10 mL) was added. The $K_3Fe(CN)_6$ (1 g, 3 mmol) was added with vigorous stirring over 3 h at 50–55°C in small portions.

After completion, the reaction mixture was evaporated in vacuum. The dry residue was treated with 15 mL water, filtered, washed with water, and dried. 6-Amino-1,3,7-triazapyrene was obtained in 95% yield (105 mg) as yellow crystals which sublimate at 250°C (EtOH). IR (neat), ν, cm^{-1}: 3,328, 3,170, 1,638, 1,613, 1,499. ^1H NMR (250 MHz, DMSO-D_6), δ, ppm: 7.65, 8.46 (two d, AB system, $J = 9.3$ Hz, 2H, H-4, H-5); 7.95, 8.88 (two d, AB system, $J = 9.0$ Hz, 2H, H-10, H-9); 7.99 (br s, 2H, NH_2); 9.15 (s, 1H, H-8); 9.44 (s, 1H, H-2). ^{13}C NMR (75 MHz, DMSO-D_6), δ, ppm: 106.9, 115.9, 116.0, 120.6, 123.5, 127.5, 131.3, 135.3, 150.6, 153.7, 155.6, 157.3, 157.6.

7.4 General Procedure for the Oxidative Alkylamination of Quinazoline [87]

To a stirred solution of quinazoline (0.130 g, 1 mmol) in the appropriate alkylamine (10 mL) at 8–10°C, $AgPy_2MnO_4$ (0.770 g, 2 mmol) was added in small portions over a 30 min−1 h period. The excess amount of the alkylamine was subsequently removed under reduced pressure. The residue was grinded with silica gel (3–4 g), brought onto a column with silica gel (3.5 × 20 cm) and purified by flash column chromatography with CH_2Cl_2−MeOH (50:1) as the eluent to yield 4-alkylaminoquinazoline. *4-Butylaminoquinazoline* was obtained in 93% yield as white solid, mp 116–118°C. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.67 (s, 1H, 2-H), 7.83 (d, $J = 8.3$ Hz, 1H, 8-H), 7.75 (d, $J = 8.3$ Hz, 1H, 5-H), 7.71 (t, $J = 7.6$ Hz, 1H, 6-H), 7.44 (t, $J = 7.6$ Hz, 1H, 7-H), 6.00 (br. s, 1H, NH), 3.67 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.72 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.47 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.98 (t, $J = 7.4$ Hz, 3H, $CH_2CH_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 158.6, 154.4, 148.2, 131.5, 127.4, 124.9, 119.6, 114.0, 40.2, 30.4, 19.2, 12.8. HRMS (ESI): calcd. for $C_{12}H_{16}N_3$ $[M+H]^+$ 202.1344; found 202.1345. $C_{12}H_{15}N_3$ (201.3): calcd. C 71.61, H 7.51, N 20.88; found C 71.92, H 7.69, N 21.03.

7.5 General Procedure for the Oxidative Alkylamination of 1,3,5-Triazine [75]

To a stirred mixture of alkylamine (5 mL) and ethanol (5 mL) at −11°C to −5°C 1,3,5-triazine (0.081 g, 1 mmol) was added. After dissolving of 1,3,5-triazine, $AgPy_2MnO_4$ (0.578 g, 1.5 mmol) was added in small portions over 40 min. Subsequently, alkylamine and ethanol were removed under reduced pressure. The residue was grinded with silica gel (3–4 g), brought onto a column with silica gel (3.5 × 25 cm), and chromatographed using CH_2Cl_2–MeOH (50:1) as the eluent,

yielding 2-alkylamino-1,3,5-triazines. For the amination and methylamination a 2N NH_3 solution in EtOH (10 mL) and a 2N methylamine solution in MeOH (15 mL) were used, respectively. *2-Amino-1,3,5-triazine* was obtained in 30% yield as white solid, mp >206°C (sublimation). ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.60 (s, 2H, H-4, H-6), 5.34 (br s, 2H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm: 165.9, 165.7. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_3H_5N_4$: 97.0514; found: 97.0511. *2-(Morpholin-1-yl)-1,3,5-triazine* was obtained in 63% yield as white solid, mp 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 8.54 (s, 2H, H-4, H-6), 3.87 [m, 4H, $O(CH_2)_2$], 3.75 [m, 4H, $N(CH_2)_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm: 165.7, 163.2, 66.6, 43.5. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_7H_{11}N_4O$: 167.0933; found: 167.0931.

7.6 Typical Procedure for Iodine-Catalyzed Amination of Benzoxazoles [102]

t-BuOOH (70% solution in water, 1 equiv., 1 mmol) was added to a well-stirred suspension of benzoxazole (1 mmol, 1 equiv.), AcOH (1.1 mmol, 1.1 equiv.), Et_2NH (1 mmol, 1 equiv.), and I_2 (0.05 mmol, 0.05 equiv.) at room temperature for 12 h. The reaction mixture was extracted with EtOAc (3 × 20 mL) and dried over Na_2SO_4, solvent was removed under reduced pressure, and the product was purified by silica gel column chromatography (EtOAc–hexane 5:95–10:90) to afford *N,N*-diethylbenzoxazol-2-amine in 95% yield as colorless liquid, R_f 0.20 (10% EtOAc–hexane). IR (neat), ν, cm^{-1}: 2,975, 2,935, 1,640, 1,580, 1,460, 1,247, 740. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.27 (t, $J = 7.2$ Hz, 6H), 3.57 (q, $J = 7.2$ Hz, 4H), 6.97 (t, $J = 7.7$ Hz, 1H), 7.13 (t, $J = 7.7$ Hz, 1H), 7.24 (d, $J = 7.9$ Hz, 1H), 7.34 (d, $J = 7.8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, ppm: 13.4, 42.9, 108.4, 115.7, 119.9, 123.7, 143.5, 148.7, 162.1. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{14}N_2O$: 191.1184; found: 191.1176.

7.7 Synthesis of 2-Aminopyridine from Pyridine N-oxide [114]

To a solution of pyridine N-oxide (190 mg, 2 mmol) and *tert*-butylamine (1.05 mL, 10 mmol) in $PhCF_3$ (10 mL) at 0°C was added Ts_2O (1.30 g, 4.0 mmol) as a solid in portions while maintaining the reaction temperature at <5°C. LC revealed incomplete conversion after 10 min. More *tert*-butylamine (0.21 mL, 2.0 mmol) was added followed by Ts_2O (0.33 g, 1.0 mmol). Complete conversion was obtained in 10 min. TFA (5 mL) was added to the reaction mixture, which was then aged at 70°C for 5 h. The solution was concentrated to oil and diluted with water (5 mL) and CH_2Cl_2 (10 mL). The pH was adjusted to ~10 with 50% aq NaOH (~4 mL). The

top aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were concentrated and chromatographed (SiO_2, 2 × 20 cm, 1−3% MeOH/CH_2Cl_2) to give 2-aminopyridine (158 mg, 84% yield). NMR data matched those of commercial material.

7.8 General Procedures for the VNS Amination of 3-Nitropyridines [138]

7.8.1 Procedure A with Hydroxylamine

The 3-nitropyridine compound (10 mmol) in ethanol (50 mL) was added dropwise to a stirred solution of hydroxylamine hydrochloride (30 mmol), potassium hydroxide (80 mmol), and zinc dichloride (10 mmol) in ethanol (100 mL). In some cases more hydroxylamine (15 mmol) and potassium hydroxide (20 mmol) were added after 5 h of stirring. The reaction mixture was stirred overnight at room temperature and poured into water (200 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic phase washed with water, dried, and evaporated to give the 2-amino-5-nitropyridine compound.

7.8.2 Procedure B with 4-Amino-1,2,4-Triazole

The 3-nitropyridine compound (10 mmol) in dimethyl sulfoxide (30 mL) was added dropwise to a stirred solution of 4-amino-1,2,4-triazole (35 mmol) and potasium *tert*-butoxide (20 mmol) in dimethyl sulfoxide (60 mL) under nitrogen atmosphere. The reaction mixture was stirred for 5 h at room temperature and then poured into water (200 mL) saturated with NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic phases evaporated, and the residue recrystallized from aqueous methanol to give the 2-amino-5-nitropyridine compound.

2-Amino-5-nitropyridine was obtained in 54% yield (method *A*) or 76% yield (method *B*) as yellow solid, mp 188–189°C. IR (KBr): 3,501, 3,363, 1,648, 1,632, 1,583, 1,570, 1,494, 1,473, 1,333, 1,285, 1,129, 842 cm^{-1}. ^1H NMR (DMSO-D_6), δ, ppm: 6.50 (d, J = 9.39 Hz, 1H, H-3), 7.52 (br s, 2H, NH_2), 8.12 (dd, J = 2.80, 9.31 Hz, 1H, H-4) 8.84 (d, J = 2.78 Hz, 1H, H-6).

In summary, one can conclude that a great progress in the S_N^H-amination has been achieved since the discovery of the Chichibabin amination reaction. Efforts of many scientists were focused on searching new methods for the C–H activation, finding more appropriate reaction conditions, expanding the range of aromatic and heteroaromatic substrates and amination agents. As a result, a great deal of new aminating reagents, auxiliary leaving groups, solvents, catalysts as well as aromatic substrates have been introduced into the practice of organic synthesis. Also

impressive was opening new reaction mechanisms for the S_N^H-amination, and there is no doubt that we can expect new ideas and practical applications in this promising area.

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Electrochemical C–H Functionalization of Arenes and Heteroarenes

Iluminada Gallardo and Gonzalo Guirado

Abstract Electrochemical methodology has been exploited to develop new synthetic routes and to rationalize the mechanism for the C–H functionalization of arenes and heteroarenes. The advantages of the electrochemical approach to perform nucleophilic aromatic substitution reactions, such as a low cost and availability of reagents, atom economy and high yields, provide an environmentally friendly way to functionalize arenes and heteroarenes.

Keywords Arenes · Cyclic voltammetry · Electrochemistry · Electrolysis · Heteroarenes · S_N^H and S_N^X reactions

Contents

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Abbreviations

Ac	Acetyl
Ar	Aryl
BDE	Bond dissociation energy
BMIM	1-butyl-2-methylimidazolium
Bu	Butyl
DDQ	2,3-dichloro-5,6-dicyano- 1,4-benzoquinone
DISP	Disproportionation mechanism. Homogeneous electron transfer
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
E	Electric potential
E^0	Standard potential
E_p	Peak potential
E_{pa}	Anodic peak potential
E_{pc}	Cathodic peak potential
ECE	Electrochemical–Chemical–Electrochemical mechanism. Heterogeneous electron transfer
ET	Electron transfer
Et	Ethyl
GC	Gas chromatography
Hex	Hexyl
I	Current
i-Pr	*iso*-propyl
L	Liter(s)
MS	Mass spectrometry
Me	Methyl
mol	Mole(s)
S_N^H	Nucleophilic aromatic substitution of hydrogen
S_N^X	Nucleophilic aromatic substitution of halogen X or other good leaving groups
NMR	Nuclear magnetic resonance
Nu	Nucleophile
Ph	Phenyl
R	Alkyl
rt	Room temperature
RTILs	Room temperature ionic liquids
s	Second(s)
SCE	Saturated calomel electrode
S_NAr	Aromatic nucleophilic substitution

t-Bu	*tert*-butyl
$TBABF_4$	Tetrabutylammonium tetrafluoroborate
THF	Tetrahydrofuran
v	Scan rate
V	Volt

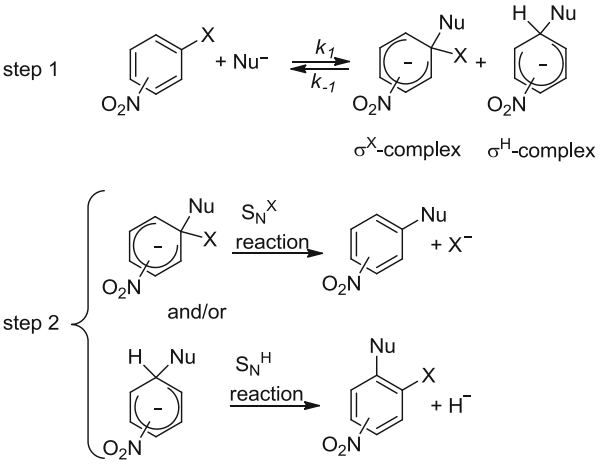
1 Introduction

There are several mechanisms for aromatic nucleophilic substitution [1–5]. It has been well established that the S_NAr mechanism is generally operating in the series of those aromatic and heteroaromatic compounds where activating groups are present in an aromatic ring. The S_NAr mechanism consists of two steps. As a result of the first step, the key intermediates, also known as σ-complexes, are formed. These σ-complexes may be of different nature, namely σ^H-complexes and σ^X-complexes. The cleavage of either C–H (in case of σ^H-complexes) or C–X bond (where X is a heteroatom in σ^X-complexes) is observed at the second step, thus giving rise to the $S_N{}^H$ or $S_N{}^X$ products, respectively. It is worth noting that either formation or decomposition of the anionic intermediates, σ-complexes, may be the rate limiting step of the reactions (Scheme 1).

Conversion of σ^X-complexes into $S_N{}^X$ products through X^- elimination is strongly dependent on the nature of the leaving group, the used nucleophilic reagent, and the effect of media, but, in general, it used to be the fast step of the reactions. The departure of the hydride anion from σ^H-complexes is a more complicated process, since it is a very poor leaving group. However, the $S_N{}^H$ reactions in which an aromatic hydrogen atom is replaced by a nucleophilic reagent are well known. Until 2001, the conversion of aromatic compounds into the $S_N{}^H$ products proved to occur by two ways: (1) through vicarious nucleophilic substitution of hydrogen, which has been extensively studied, especially in case of carbanionic nucleophiles [4–15]; (2) by means of chemical oxidation of intermediate σ^H-complexes [16–20]. Indeed, rearomatization of σ^H-complexes through formal displacement of H^- is a process which requires an appropriate chemical oxidant.

One of the relatively new approaches is electrochemical oxidation. Terrier and co-workers [21], using electrochemical methods, have established the reaction mechanism leading to the rearomatized products for 2-nitropropenide adducts of nitrobenzofuroxans and nitrobenzofurazans. In 2001, in the molecular electrochemistry laboratory of the University Autonomous of Barcelona (UAB), it was demonstrated that electrochemical methods proved to be a powerful tool to study the following aspects of the S_NAr reactions: (a) to establish the mechanism of electrochemical oxidation of σ^H- and σ^X-complexes [22, 23]; (b) to determinate the efficiency of nucleophilic aromatic substitution reactions (determining the type of adducts which were present in solutions, σ^H- and σ^X-complexes, and their relative proportions) [22, 23]; (c) to obtain S_NAr products in good preparative yields [22–28], (d) to force nucleophilic substitution of hydrogen to occur [29], and

Scheme 1 Plausible mechanisms for S_NAr reactions



(e) to perform a thermodynamic elucidation of σ^H-complexes, as intermediates of the S_N^H reactions [30].

2 Mechanisms for Electrochemical Oxidation of σ-Complexes

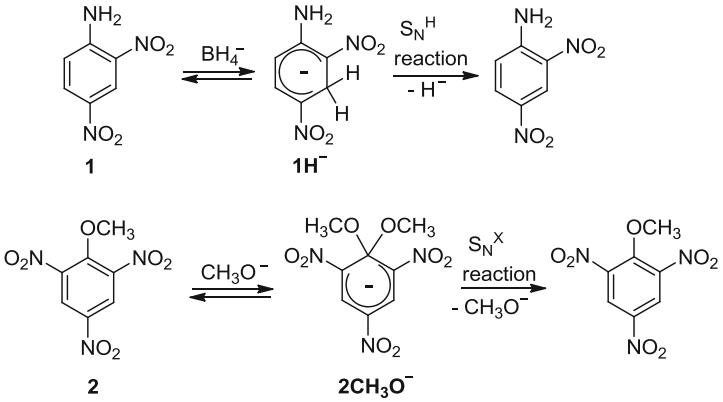
The σ^H-adduct (with H^- as nucleophile, $\mathbf{1H^-}$) and the σ^X-complex (with CH_3O^- as nucleophile, $\mathbf{2CH_3O^-}$) of 2,4-dinitroaniline and 2,4,6-trinitroanisole, respectively, were chosen as model compounds to establish the mechanism of electrochemical oxidation (Scheme 2). These compounds, $\mathbf{1H^-}$ and $\mathbf{2CH_3O^-}$, can be isolated as pure crystalline compounds in the form of tetramethylammonium [14, 15] and potassium [31] salts, respectively.

The combined use of cyclic voltammetric analysis (**1**, $\mathbf{1H^-}$, **2**, and $\mathbf{2CH_3O^-}$solutions) and controlled-potential electrolysis ($\mathbf{1H^-}$, and $\mathbf{2CH_3O^-}$solutions), as electrochemical methods [32, 33], allows the mechanism for electrochemical oxidation of these σ-complexes in DMF + 0.1 M $TBABF_4$ to be established.

2.1 Electrochemical Oxidation of σ^X-Complexes

Cyclic voltammograms[1] for the compound $\mathbf{2CH_3O^-}$ at low and fast scan rates are shown in Fig. 1a, b. At low-scan rates (Fig. 1a), no reduction waves have been

[1] The experimental cyclic voltammograms of Fig. 1 were also simulated (Digisim Software) [23].



Scheme 2 Model compounds used to elucidate $S_N{}^H$ and $S_N{}^X$ mechanisms

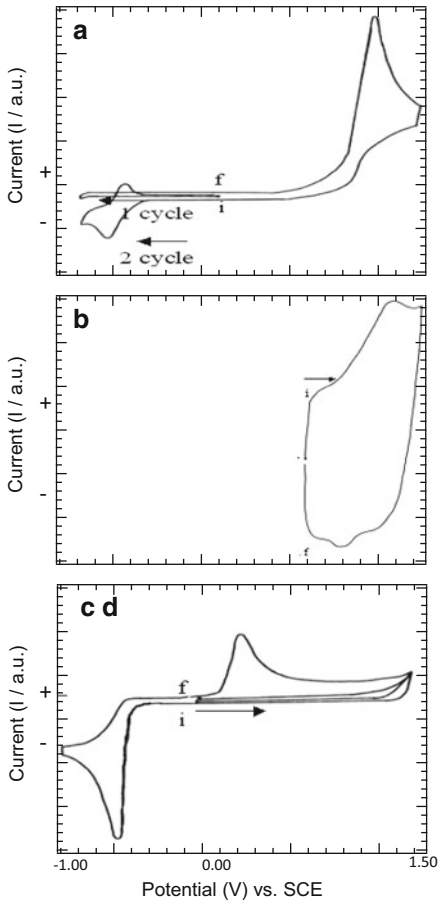


Fig. 1 Cyclic voltammetry (arbitrary I units). Two cycles. Scan potential range: 0.00 to −0.50 to 1.50–0.00 V. (**a**) $2CH_3O^-$, 1.0 V s^{-1}; (**b**) $2CH_3O^-$, 16 000 V s^{-1}; (**c**) $2CH_3O^-$, 1.0 V s^{-1}, after electrolysis (1.3 V, 1 F); (**d**) 2,4,6-trinitroanisole, 1.0 V s^{-1}

observed for the first cathodic scan, whereas an irreversible one-electron oxidation wave appears in the oxidation scan (ca. 1.12 V). In the second cathodic scan, a reduction wave (ca. −0.73 V) is observed. This reduction wave corresponds to the product formed in the first anodic process.

The peak current value for the oxidation wave [analyzed by comparison with the oxidation of *tris*(4-bromophenyl)-amine] corresponds to a one-electron process. The shape of the voltammogram (peak width) indicates that the step of electron transfer is fast and does occur under kinetically controlled chemical reaction [32]. The peak potential is not dependent on the concentration in the range 2–20 mM, and the peak potential variation with scan rates is 35 mV by unit log *v* (scan rate).

At $v \geq 16{,}000$ V s^{-1} (Fig. 1b), the voltammogram of $\mathbf{2CH_3O^-}$ presents a single reversible oxidation one-electron wave ($E^0 = 1.20$ V). Thus, it could be concluded that the initially produced radical reacts according to the first order chemical reaction through a stepwise EC mechanism.

The first step involves the departure of one electron from the σ^X-complex, $\mathbf{2CH_3O^-}$, and it leads to the formation of the corresponding radical species, $\mathbf{2CH_3O^{\cdot}}$. This radicals undergo the first order C–O bond cleavage to give the final rearomatized product, 2,4,6-trinitroanisole. In all cases where $\mathbf{CH_3O^{\cdot}}$ must be produced, dismutation to methanol and formaldehide is postulated [34, 35].

After controlled-potential electrolysis (at 1.3 V and 1 F) of $\mathbf{2CH_3O^-}$ solution, cyclic voltammetric analysis of the reaction mixture (Fig. 1c) indicated that 2,4,6-trinitroanisole was the only final product formed, and it was produced in quantitative yield. In the first anodic scan, the oxidation wave, at 1.12 V, does not exist; only after cathodic reduction, the product formed has a new oxidation wave (ca. 0.2 V). The same behavior is shown by an authentic sample of 2,4,6-trinitroanisole (Fig. 1d). Furthermore, the final 2,4,6-trinitroanisole was identified by GC-MS, ^{1}H NMR, and ^{13}C NMR analyses.

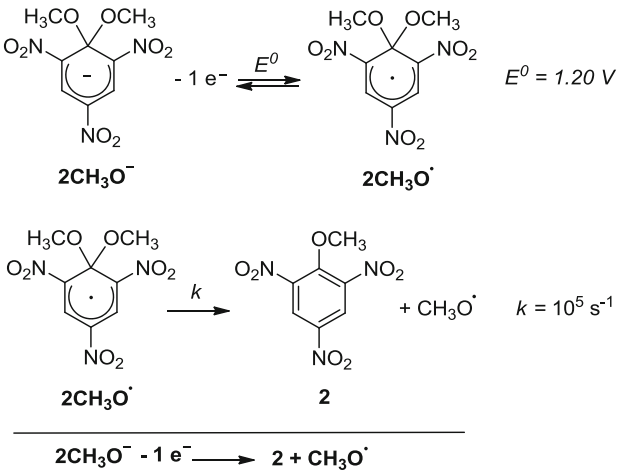
In summary, these experimental results show that, after exhaustive oxidation of $\mathbf{2CH_3O^-}$, the re-aromatized 2,4,6-trinitroanisole is obtained. The voltammograms show that oxidation of σ^X-complexes $\mathbf{2CH_3O^-}$occurs through a two-step mechanism (stepwise EC mechanism): a fast electron transfer on the electrode, and a chemical reaction that is the rate determining step (Scheme 3).

It is worth to note that 2,4,6-trinitroanisole is obtained after the loss of just one electron by one mol of $\mathbf{2CH_3O^-}$ (S_NAr reaction).

2.2 *Electrochemical Oxidation of σ^H-Complexes*

Cyclic voltammograms[2] for compound $\mathbf{1H^-}$ at low and fast scan rates are shown in Fig. 2a, b. At low-scan rates (Fig. 2a) no reduction waves have been observed in the first cathodic scan, whereas an irreversible two-electron oxidation wave appears in

[2] The experimental cyclic voltammograms of Fig. 2 were also simulated (Digisim Software) [22].



Scheme 3 The EC mechanism for electro-oxidation of the σ^X-complex $\mathbf{2CH_3O^-}$

the oxidation scan (ca. 0.30 V). On the second cathodic scan, a reduction wave (ca. −1.03 V) is observed. This reduction wave, at −1.03 V, corresponds to the product formed in the first anodic process.

The current peak value for the oxidation wave [analyzed by comparison with the oxidation of *tris*(4-bromophenyl)amine] corresponds to a two-electron process. The shape of the voltammogram (peak width) indicates that the electron transfer is fast and takes place under kinetically controlled chemical reaction [32]. The peak potential is not concentration dependent (in the range 2–20 mM), and the peak potential variation with scan rates is 35 mV by unit log v (scan rate).

At $v \geq 380$ V s^{-1} (Fig. 2b), the voltammogram of $\mathbf{1H^-}$ presents a single reversible oxidation one-electron wave ($E^0 = 0.325$ V). It is (if there are no chemical reactions) linked with electron transfer, and a one-electron wave is observed.

After controlled-potential electrolysis (at 0.50 V and 2 F) of $\mathbf{1H^-}$ solution, cyclic voltammetric analysis of the reaction mixture (Fig. 2c) indicates that 2,4-dinitroaniline is the only final product formed, and it is produced in the quantitative yield. The same behavior has been shown by an authentic sample of 2,4-dinitroaniline (Fig. 2d). Furthermore, the final 2,4-dinitroaniline was identified by GC-MS, ^{1}H NMR, and ^{13}C NMR analyses.

In summary, the experimental results show that after exhaustive oxidation of the adduct $\mathbf{1H^-}$, 2,4-dinitroaniline is obtained as a result of the formal loss of two electrons and a proton [Eq. (4) of Scheme 4]. The voltammograms show that oxidation of σ^X-complex $\mathbf{1H^-}$ takes place through a three-step mechanism: a fast electron transfer on the electrode, a chemical reaction, and the second electron transfer in solution (DISP mechanism), or on the electrode (the ECE mechanism) [32].

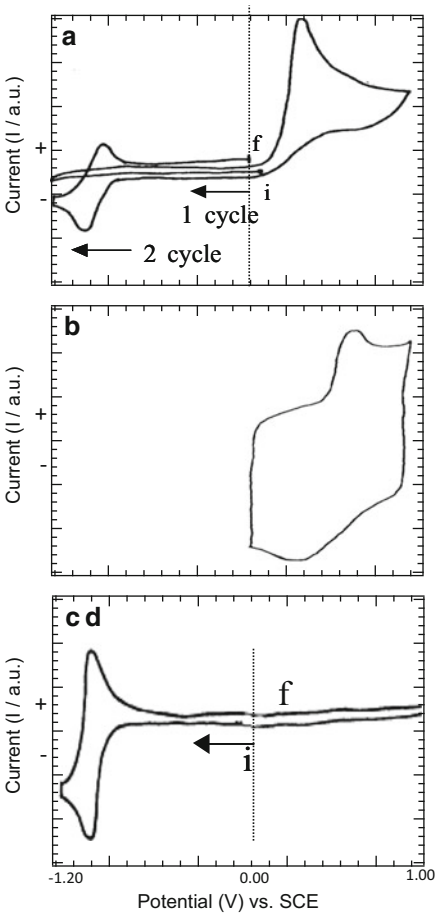
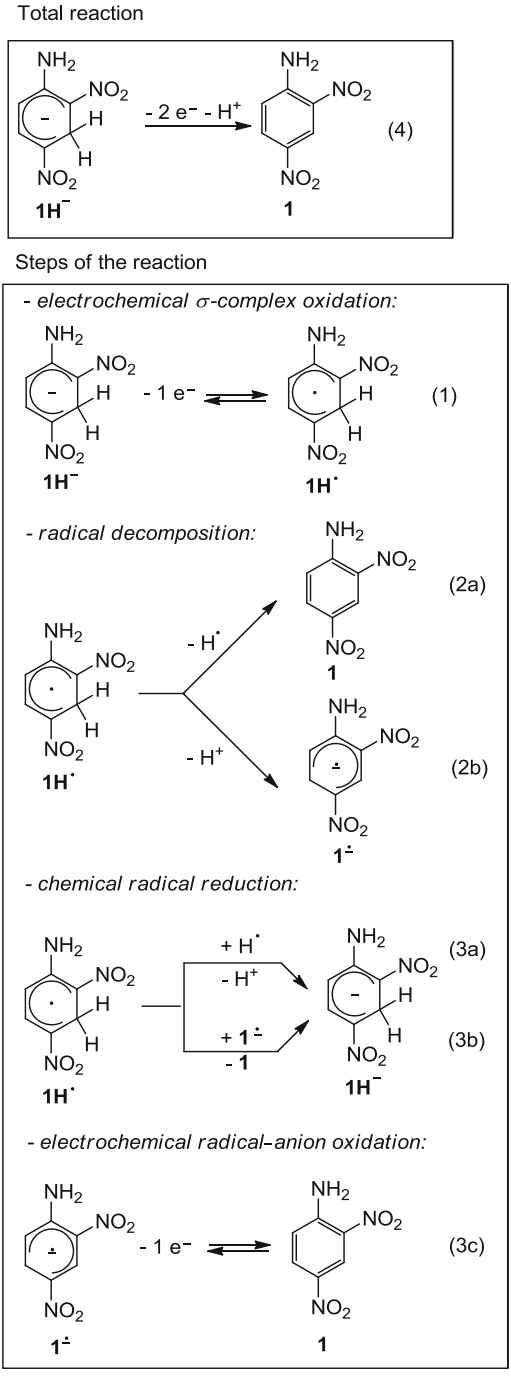


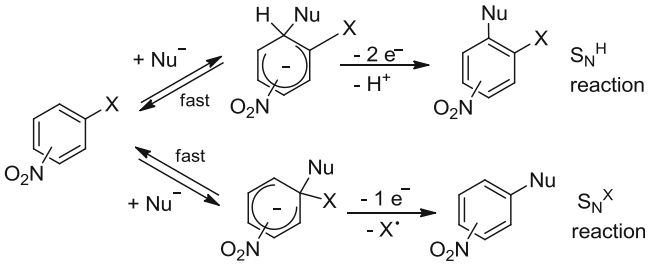
Fig. 2 Cyclic voltammetry (arbitrary I units). Two cycles. Scan potential range: 0.00 to −1.00 to 0.75–0.00 V. (**a**) $1H^-$, 1.0 V s^{-1} (two cycles); (**b**) $1H^-$, 380 V s^{-1}; (**c**) $1H^-$, 1.0 V s^{-1}, after electrolysis (0.5 V, 2 F); (**d**) 2,4-dinitroaniline, 1.0 V s^{-1}

Three mechanistic, kinetically equivalent, hypotheses have been formulated: Eqs. (1)/(2a)/(3a), (1)/(2b)/(3b), and (1)/(2b)/(3c). In all cases the first step [Eq. (1)] involves the loss of one electron by the σ^H-complex $\mathbf{1H^-}$, with the formation of the corresponding radical $\mathbf{1H^{\cdot}}$. This radical undergoes the fist-order C–H bond cleavage to give 2,4-dinitroaniline and a hydrogen atom [Eq. (2a)], as proposed by Terrier for the related systems [21], or the radical-anion of 2,4-dinitroaniline and a proton [Eq. (2b)], as earlier proposed by Sosonkin et al. [36]. The final oxidation of hydrogen [Eq. (3a)] can be performed by the radical $\mathbf{1H^{\cdot}}$, while oxidation of the radical-anion of 2,4-dinitroaniline [Eq. (3b, 3c)] can be performed by the $\mathbf{1H^{\cdot}}$ or by electrode, respectively. However, it is accepted[3] [22, 37] that compound $\mathbf{1H^-}$ is transformed according to the mechanism described

[3] The C–H acidity of cyclohexadienyl radicals of $1H^{\cdot}$ type, where the corresponding aromatic radical-anion is stabilized by electron attracting groups, is very significant [36].

Scheme 4 The ECE/DISP mechanism for oxidation of the σ^H-complex $\mathbf{1H^-}$





Scheme 5 Electrochemically promoted $S_N{}^H$ and $S_N{}^X$ reactions

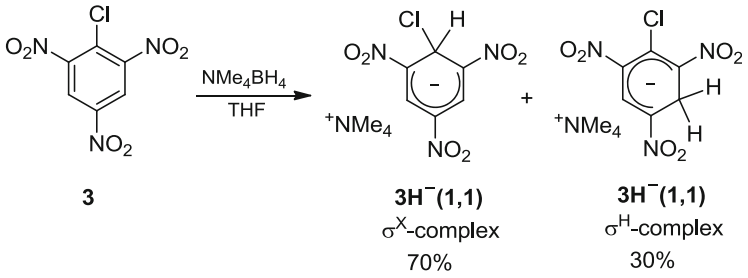
by Eqs. (1)/(2b)/(3b), or (1)/(2b)/(3c). In spite of the relatively fast cleavage of $\mathbf{1H}^{\cdot}$ ($k \sim 10^3\ s^{-1}$), there are no experimental data providing unequivocal evidence for disproportionation mechanism (DISP)/Electrochemical-Chemical-Electrochemical mechanim (ECE) (Eqs. (1)/(2b)/(3b)/Eqs. (1)/(2b)/(3c)) for the last step of the reaction [38]. It should be noted that 2,4-dinitroaniline is formed by the loss of two electrons from the compound $\mathbf{1H}^-$ (the $S_N{}^H$ reaction).

2.3 *Electrochemical Oxidation of Mixtures of σ^H- and σ^X-Complexes*

Since the mechanism for electrochemical oxidation of σ^H- and σ^X-complexes involves either two electrons ($S_N{}^H$ reaction) or one electron ($S_N{}^X$ reaction), respectively (Scheme 5), it is possible to determine their relative concentrations in a mixture of σ-complexes by direct measuring the peak current values on voltammograms.

This situation is exemplified by the reaction of 1-chloro-2,4,6-trinitrobenzene with the hydride anion (Scheme 6). The compound $\mathbf{3H}^-$ [39] is formed as a 30:70 mixture of 1,1-dihydro-3-chloro-2,4,6-trinitrocyclohexadienyl $\mathbf{3H}^-(\mathbf{1,3})$ and 1-chloro-1-hydro-2,4,6-trinitrocyclohexadienyl $\mathbf{3H}^-(\mathbf{1,1})$ tetramethylammonium salts. A freshly prepared sample of the compound $\mathbf{3H}^-$ was used in the electrochemical studies [23].

Figure 3 shows a cyclic voltammogram for compound $\mathbf{3H}^-$ at a low-scan rate (see footnote 1). In all cases, starting with a cathodic scan, no reduction waves appear in the first scan, so neither 1-chloro-2,4,6-trinitrobenzene (the $S_N{}^H$ product), nor 1,3,5-trinitrobenzene (the $S_N{}^X$ product), are initially present in the reaction mixtures. Figure 3a shows that, upon starting with an anodic scan, two well-defined waves at 0.68 V and 1.24 V are observed. When the anodic scan is followed by a cathodic scan, two waves, at −0.53 V and −0.56 V, are observed. These reduction waves correspond to 1-chloro-2,4,6-trinitrobenzene (the $S_N{}^H$ product) and 1,3,5-trinitrobenzene (the $S_N{}^X$ product), respectively [23, 40].



Scheme 6 The formation of σ-complexes of 1-chloro-2,4,6-trinitrobenzene with the hydride anion H^- as nucleophile

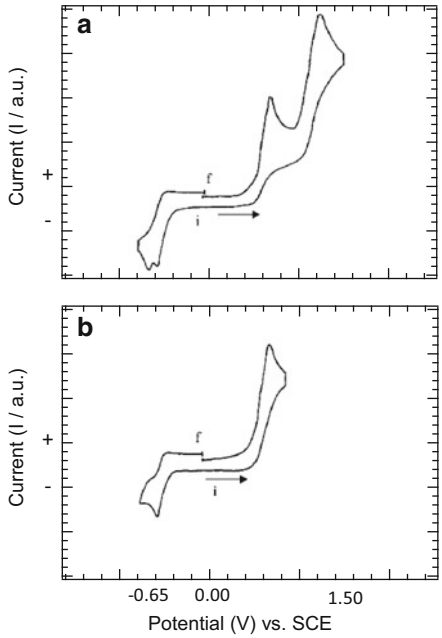
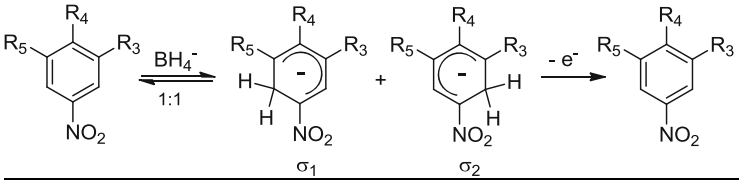


Fig. 3 Cyclic voltammetry (arbitrary I units). (**a**) $\mathbf{3H}^-$ [mixture $\mathbf{3H}^-$(**1**,**3**) and $\mathbf{3H}^-$(**1**,**1**)], 1.0 V s^{-1}. The scan is performed in the potential range from 0.0–1.5 to −1.0 to 0.0 V; (**b**) $\mathbf{3H}^-$ [mixture $\mathbf{3H}^-$(**1**,**3**) and $\mathbf{3H}^-$(**1**,**1**)], 1.0 V s^{-1}. The potential scan range is from 0.0–1.0 to −1.0 to 0.0 V

When the anodic scan is reversed after the first oxidation wave (0.68 V) (Fig. 3b) only one reduction wave is obtained (−0.53 V). Thus, the oxidation wave at 1.24 V appears to be connected with the reduction wave at −0.56 V. That, is to say, 1-chloro-2,4,6-trinitrobenzene is obtained due to the oxidation of $\mathbf{3H}^-$(**1**,**3**) (σ^H-complex, the $S_N{}^H$ reaction), while 1,3,5-trinitrobenzene is derived from the oxidation of $\mathbf{3H}^-$(**1**,**1**) (σ^X-complex, the $S_N{}^X$ reaction).

It follows from the voltammogram (Fig. 3a) that the ratio of [σ^H-complex]: [σ^X-complex] = 30:70, which is in good agreement with that reported in the

Table 1 Electrochemical characteristics for σ^H-complexes and reaction products with the hydride anion H^-as nucleophile



R_3	R_4	R_5	$E_{pa}(\sigma_1)^{a,b}$ (V) (%)[c]	$E_{pa}(\sigma_2)^{a,b}$ (V) (%)[c]	$E^{0\ a,d}$ (oxidation product)[e] (V)
CN	H	H	0.19 (100%)	–	−0.90
NO_2	H	H	0.39 (100%)	–	−0.82
NO_2	CH_3	H	–	0.25 (100%)	−0.96
NO_2	OCH_3	H	–	0.30 (100%)	−1.00
NO_2	F	H	0.44(20%)	0.33(80%)	−0.79
NO_2	Cl	H	0.44(22%)	0.32(70%)	−0.78
NO_2	Br	H	0.44(30%)	0.32(70%)	−0.78
NO_2	NH_2	H	–	0.30(100%)	−0.95
NO_2	H	CN	0.60(100%)	–	−0.62
NO_2	H	NO_2	0.77(100%)	–	−0.58
NO_2	CH_3	NO_2	0.62(100%)	–	−0.68

[a]All the potentials are given vs. SCE reference electrode
[b]Peak potentials obtained by cyclic voltammetry when two isomeric adducts were formed, E_{pa} were assigned on the basis of analytical and ^{1}H NMR data [35, 38]
[c]Yields of σ-complexes
[d]Standard potential of oxidation product [35, 40]
[e]The S_N^H products (100% yields) were obtained by exhaustive electrolysis of the σ^H-complexes (E_{pa} +0.1 V, 2 F). The oxidation products were analyzed by cyclic voltammetry, GC/MS and ^{1}H NMR

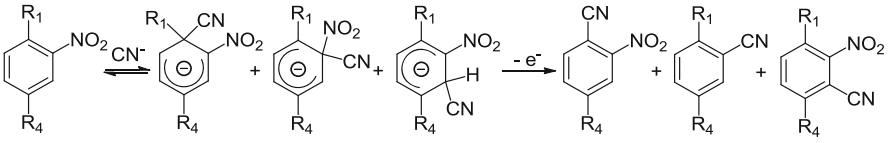
literature [39]. Then, you can determine a number of σ-complexes formed and their concentrations. Using appropriate potentials, the electrolysis of σ-complexes can give rise to either S_N^H products or both S_N^H and S_N^X products.

2.4 *Electrochemical Features of σ^H- and σ^X-Complexes*

Two series of compounds were prepared in order to distinguish the electrochemical behavior of σ^H- and σ^X-complexes. The first one, σ^H-complexes (H^- as nucleophile) of nitroaromatic compounds with a different number of nitro groups in the ring (Table 1) [22]. The second one, σ^H- and σ^X-complexes of nitroaromatic compounds with diverse leaving groups (Table 2) [23].

The σ^H-complexes (H^- as nucleophile) were prepared by stoichiometric addition of tetramethylammonium borohydride to solutions of nitroarenes in DMF + 0.1 M $TBABF_4$ under inert atmosphere. The electrochemical experiments (cyclic voltammetry and electrolysis) are analogous to those which have been described for **1H**$^-$ (Sect. 2.2). The results are summarized in Table 1.

Table 2 Electrochemical characteristics for σ-complexes and reaction products with the cyanide ion as nucleophile



R_1	R_4	Nu/Ar[a]	σ (%)	$E_{pa}(\sigma_1)$[b] (V)	$E_{pa}(\sigma_2)$[b] (V)	$E_{pa}(\sigma_3)$[b] (V)	1^{c-e} (%)[f]	2^{c-e} (%)[f]	3^{c-e} (%)[f]
H	CN	2	70	0.65	0.94	–	45	50	–
H	CF_3	2	50	0.58	0.86	–	35	27	–
OCH_3	NO_2	1	40	0.83	0.60	0.61	26	26	15
Cl	NO_2	1	58	1.38[g]	–	0.59	25	–	7

[a]Molar ratio of nucleophile (Nu) and nitroarene (Ar)
[b]All potentials are given vs. SCE reference electrode
[c]The S_NH and S_NX products were obtained by exhaustive electrolysis at E_{pa} + 0.1 V
[d]The oxidation products were analyzed by cyclic voltammetry, GC/MS and ^{1}H NMR
[e]Blank reactions (without oxidation of mixture) led to less than 10% yields of substitution products
[f]This yield is calculated on the σ-complex formed. The remainder relates to recovered reactants
[g]Excess of the cyanide can be eliminated by electrochemical oxidation at 1.33 V

Quantitative (100%) yields for the formation of σ^H-complexes were observed, since no reduction waves for nitroarenes have been observed in the first cathodic scan. When two σ^H-complexes are present in solution, two waves in the first anodic scan have to appear (two-electron-irreversible oxidation wave for each compound). For 1-fluoro-2,4-dinitrobenzene, 1-chloro-2,4-dinitrobenzene, and 1-bromo-2,4-dinitrobenzene, two types of σ^H-complexes have been identified, probably 1,3- and 1,5-adducts. The oxidation peak potential (E_{pa}) is mainly dependent on the number of electron-withdrawing groups: E_{pa} increases with the number of nitro- or cyano groups available in an aromatic ring. Exhaustive electrolysis of σ^H-complexes (by the loss of two electrons and one proton) leads to the corresponding nitroarene in 100% yield.

The σ-complexes of nitroaromatic compounds with the cyanide ion were prepared by stoichiometric addition of CN^- to solutions of nitroarenes in DMF + 0.1 M $TBABF_4$ under inert atmosphere. The electrochemical experiments (cyclic voltammetry and electrolysis) are analogous, as it has been described for **3H**$^-$ (Sect. 2.3). The results are summarized in Table 2.

It is important to underline that the oxidation peak potentials of σ^X-complexes are higher than those of σ^H-complexes, and the oxidation peak potential is dependent on the nature of the leaving group. Indeed, for Cl^- the potential is ~1.35–1.40 V, for CH_3O^- it is ~0.90–1.00 V, and for NO_2^- it is ~0.60–0.80 V. All electrolyses have been carried out at a potential higher than E_{pa} of the corresponding σ^X-complex, and the assembly implying that the S_NH and S_NX products are recovered.

In summary, the use of electrochemistry allows: (a) determining the type of σ-complexes which are present in the solution (number of waves, peak potential wave) and their relative amounts (intensity of peak wave), (b) establishing the oxidative conversion of the σ-complexes into re-aromatized nitroaromatic compounds by observing the reduction in the re-aromatized products, and (c) achieving the final substitution products by performing exhaustive electrolysis of solutions of σ-complexes at a precise value of applied potential.

3 Synthetic Applications of Electrochemical S_N^H Reactions

Until now, the electrochemical methodology described has been useful to establish the S_N^H and S_N^X reaction mechanisms. However, (a) the replacement of a hydrogen atom by another one (the hydride ion H^-as nucleophile), although being very efficient, has no synthetic value [22], and (b) the use of halogenated aromatic compounds as staring materials in the S_NAr reactions realized by electrochemical methods does not provide advantages over the conventional chemistry [23]. Meanwhile, it is possible to obtain a variety of S_N^H products by using nucleophiles other than the hydride ion [24–28].

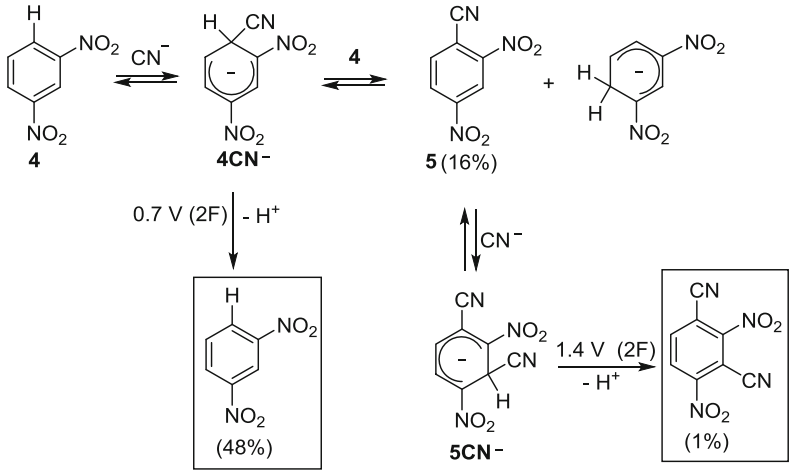
3.1 Cyanation Reactions

The cyanide anion has a strong tendency to attack non-substituted positions in aromatic rings [6, 7]. Therefore, the use of electrochemical methods described in Sect. 2.2 seems to be an appropriate approach for the S_N^H cyanation of arenes [22].

The σ^H-complexes formed by the addition of CN^- to nitroarenes (mono-, di-, and tri-nitro derivatives) have been obtained in good yields (38–46%). The electrochemical oxidation of these σ^H-complexes leads to re-aromatized compounds as a result of departure of two electrons and a proton, thus formally corresponding to the formal loss of H^- (Scheme 7, Table 3). The reaction is very clean, recovering only the starting material in addition to the reaction products. Yields are varied from 35 to 86%; where a low yield of the S_N^H product is obtained (<15%), the S_N^X product is formed in approximately 30% yield.

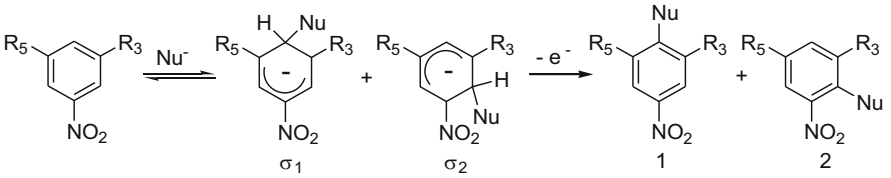
Scheme 7 explains the reactivity of 1,3-dinitrobenzene in the presence of CN^- as nucleophile, and the general character of the process. The first step is a reversible addition of CN^- to 1,3-dinitrobenzene, resulting in the formation of σ^H-complex **4CN**$^-$ (yield 50%). This σ^H-complex, being reacting with 1,3-dinitrobenzene, is converted into re-aromatized 2,4-dinitrobenzonitrile, as a result of the thermal process (yield 16%) [41].

2,4-Dinitrobenzonitrile reacts with an excess of CN^- as nucleophile to give a new σ^H-complex **5CN**$^-$. The σ^H-Complexes **4CN**$^-$and **5CN**$^-$ can be oxidized electrochemically with the formal loss of two electrons and a proton (at +0.70



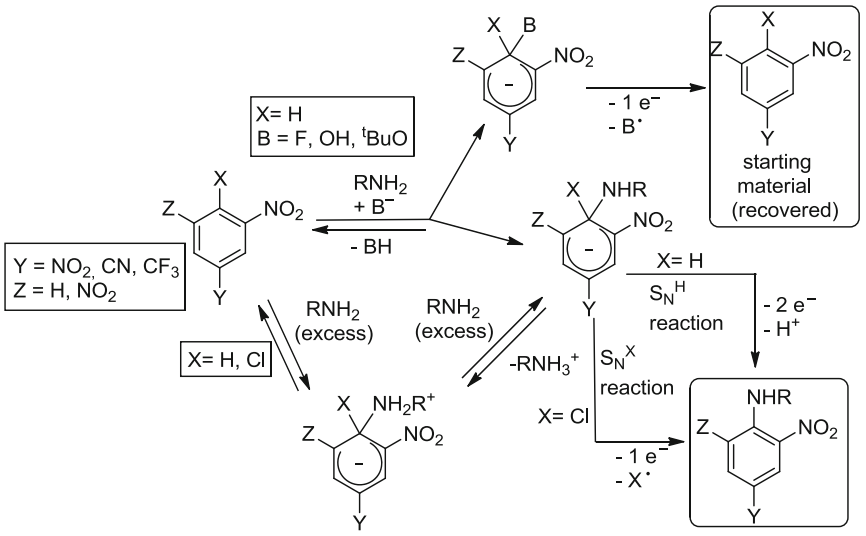
Scheme 7 Chemical and electrochemical synthesis of 2,4-dinitrobenzonitrile and 2,4-dinitroisophthalonitrile

Table 3 Yields of products obtained by electrochemical oxidation of σ^H-complexes of nitroarenes with various nucleophiles



R_3	R_5	Nu^-	Nu^-/Ar[a]	1[b] (%)[c]	2[b] (%)[c]
NO_2	NO_2	CN^-	1	60	–
		$BuNH_2$	3	30	–
		$CH_3COCH_3/tBuO^-$	[d]	60	–
		$Bu^-(BBu_4^-)$	1([e])	−(79)	−(14)
NO_2	H	CN^-	1	48	–
		$BuNH_2/tBuO^-$	[f]	39(49)	–
		$CH_3COCH_3/tBuO^-$	[d]	80	–
		$Bu^-(BBu_4^-)$	1([e])	43(30)	30(−)
H	H	CN^-	1	–	–
		$BuNH_2/tBuO^-$	[f]	–	–
		$CH_3COCH_3/tBuO^-$	[d]	80	–
		BuLi(BuMgCl)	1	41(40)[g]	−(35)[g]

[a]Molar ratio of nucleophile (Nu^-) and nitroarene (Ar)
[b]The oxidation products were analyzed by cyclic voltammetry, GC/MS and ^1H NMR
[c]This yield is calculated on the σ-complex formed. The remainder relates to reactants recovered
[d]DMF: acetone = 3:3 mL; Nitroarene: t-BuO^- = 1:1
[e]$[Me_4NBBu_4]$ = 0.05–0.20 M
[f]Nitroarene: amine: t-BuO^- = 1:5:2
[g]Also, 2,4-dibutylnitrobenzene is formed in 47% (BuLi) and 10% (BuMgCl) yields



Scheme 8 Electrochemical synthesis of amino substituted nitroarenes

and +1.40 V, respectively), thus affording 2,4-dinitrobenzonitrile (48%) and 2,4-dinitroisophthalonitrile (5%), as the final products. These results, obtained by the joint use of cyclic voltammetry and exhaustive controlled-potential electrolysis, indicate that the oxidation of σ^H-complexes appears to be a new effective approach for cyanation of nitroarenes. Table 3 shows that 2,4,6-trinitrobenzonitrile is derived in 60% yield from a similar S_N^H reaction.

3.2 *Amination Reactions*

A variety of methods for the direct amination of nitrobenzene, that do not require halogenated aromatic compounds, have been reported, including both vicarious (eliminative) [16, 17, 19, 42] and oxidative versions of nucleophilic substitution of hydrogen. Recently, we have described the amination of 1,3-dinitrobenzene promoted by fluoride ions through photochemical activation [43]. Also, the use of $KMnO_4$ as oxidant is of great practical value [3, 44].

An alternative way to achieve the direct amination of nitroaromatic compounds by using the S_N^H methodology is based on the application of the electrochemical technique (Scheme 8). For this purpose [24], we used two amines (*n*-$BuNH_2$, and *n*-$HexNH_2$), and acetamide ($AcNH_2$) in both the presence and without of different bases (*t*-BuOK, $Bu_4NF.3H_2O$, and Me_4NF). An excess of RNH_2 was varied to optimize the formation of σ^H-complexes of nitroaromatic compounds, and to minimize further amination of the S_N^H products (Table 3). A large excess of amine was used in the reaction with nitrobenzene in order to

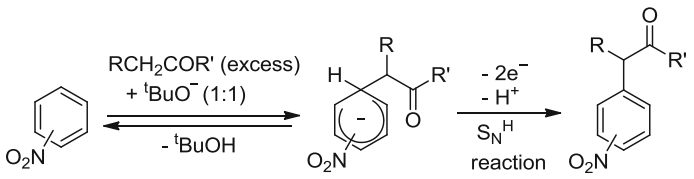
promote a nucleophilic attack leading to σ^H-complexes. In the presence of base, this percentage increases considerably (60–100%). However, this is not only due to the attack by a deprotonated nucleophile (RNH^-), but also due to the presence of an excess of base. It is remarkable that, both in the presence of external base or without it, the reaction is rather selective. Yields of the $S_N{}^H$ product, derived from the oxidative electrochemical substitution of hydrogen are ranged from fair to good (35–98%), with the exception of N-butyl-3-chloro-2,6-dinitroaniline (15%). In this case, only the starting material (1-chloro-2,4-dinitrobenzene) was recovered as a result of the electrochemical oxidation process.

The reaction of nitroarenes with an excess of nucleophile (RNH_2) (without a base) begins with the formation of a zwitterionic complex at the first step. In the presence of nucleophile (RNH_2) and base the σ-complexes are formed directly. The ratio of σ^H- or σ^X-complexes depends on the nature of substituents. The σ^H-complexes, as the key intermediates, can eliminate two electrons and a proton to give rise to the $S_N{}^H$ products, while the σ^X-complexes, by loss of an electron and $X^{\cdot}$, can be transformed into the $S_N{}^X$ product. The $S_N{}^H$ products are formed through selective electrochemical oxidation (lower oxidation potential of the intermediates) or from the $S_N{}^X$ compounds. An excess of amine present in the reaction mixture is not oxidized because the oxidation potentials for primary amines are about 1.50 V. The oxidation potential peaks for σ-complexes are lower in all cases. Finally, a comparison of chemical [42, 43] and electrochemical oxidation reactions shows that the electro-oxidation is a more convenient process in those cases when the oxidation peak potentials for σ^H-complexes are more positive than 0.6 V.

3.3 C-Arylation of Ketones

A few examples of the S_NAr reactions on nitroaromatic compounds using anions derived from ketones as nucleophiles can be found in the literature [44]. In particular, the direct coupling of carbon nucleophiles, including ketones, with nitroaromatic compounds in the presence of $KMnO_4$ has recently been described [45]. Also, a photochemical procedure, that despite reasonable yields of nitroaromatic ketones needs special conditions to achieve a good reproducibility, has been reported [18]. Although one of the best alternative to oxidative C-arylation of ketones is vicarious nucleophilic substitution [7], the latter approach fails with nitrobenzene as a substrate, and in all cases an auxiliary leaving group is necessary [46–48]. The formation of O-adduct between acetophenone enolate anion and 1,3,5-trinitrobenzene has been reported [49]. This O-adduct was converted into the corresponding C-adduct, in changing the temperature from −50 to 20ºC.

Synthesis of aromatic ketones, including those derived from mononitrobenzenes, can be achieved in good yields (60–90%) by using controlled-potential electro-oxidation of the corresponding σ^H-complexes [25]. These σ^H-complexes are formed (yields from 50 to 100%) with an excess of ketone and a strong base



Scheme 9 Electrochemical synthesis of nitroaromatic ketones

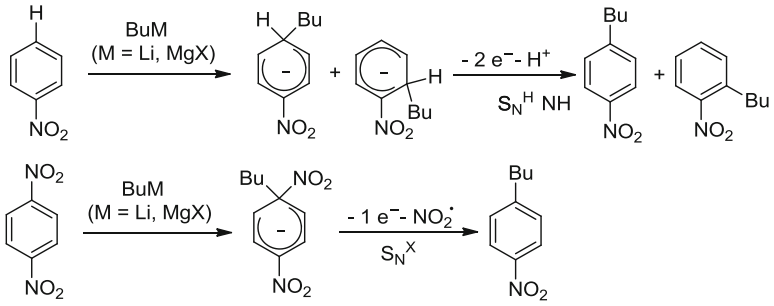
(*t*-BuOK); the latter is necessary to generate a ketone carbanion (Table 3). Good selectivity and high yields of substitution products have been obtained from the reactions of acetone, 2-butanone, and acetophenone with aromatic compounds bearing one, two, and three nitro groups.

Scheme 9 outlines the electrochemical S_N^H reaction. The intermediate σ^H-complex is formed at the first equilibrium step of the reaction between a nitroaromatic compound and ketone (taken in an excess) in the presence of a strong base. Due to the loss of two electrons and one proton (formally the hydride anion) the σ^H-complex is transformed into substitution product. Use of electrochemical methods to oxidize the intermediate σ^H-complexes at the selected potentials allows to obtain not only the desired substitution products, but also to recover the starting materials.

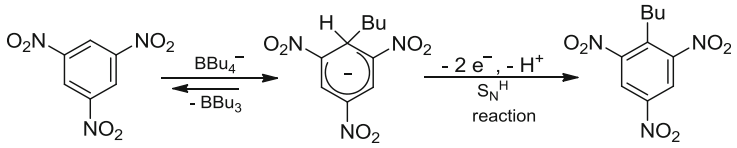
Finally, yields of products obtained electrochemically appear to be better than those from chemical reactions [44].

3.4 Alkylation Reactions with Organometallic Reagents RM and Tetraalkylborates as Nucleophiles

The well-spread industrial process to obtain alkyl substituted nitroaromatic compounds is based on the electrophilic nitration reaction. Since this process is poorly selective, and requires rather drastic conditions [50], a number of alkylation methods have been suggested [2, 3, 51, 52]. Organolithium or organomagnesiun compounds appear to be appropriate reagents to react with nitroaromatics into alkylnitroarenes through the nucleophilic substitution process S_NAr [7, 53–55]. Nevertheless, these reactions are difficult to control [56–58]. Indeed, alkyl lithium or alkyl Grignard reagents (RLi or RMgX, R = Me, Et, Bu) have been found to react with 1,3,5-trinitrobenzene in THF to afford 1,3,5-trialkyl-2,4,6-trinitrobenzene after acidification of the reaction mixture [56–58]. A similar behavior was found for 1,4-dinitrobenzene and 1-chloro-2,4-dinitrobenzene. In case of nitrobenzene the reactions lead to the mixtures of alkyl nitrobenzenes and alkyl nitrosobenzenes [59–61]. We used several oxidants, however the reactions with Br_2 and $KMnO_4$ proved to be unselective ones [62], while in the presence of rather expensive DDQ the same reactions gave rather good yields of the substitution products [63]. In the reaction of 1,4-dinitrobenzene with alkylboranes, proceeding in *t*-BuOH in the presence of *t*-BuOK, alkylnitrobenzenes have been obtained in



Scheme 10 Electrochemical synthesis of alkyl substituted nitroaromatic compounds by the reaction of nitrobenzenes with organometallic reagents



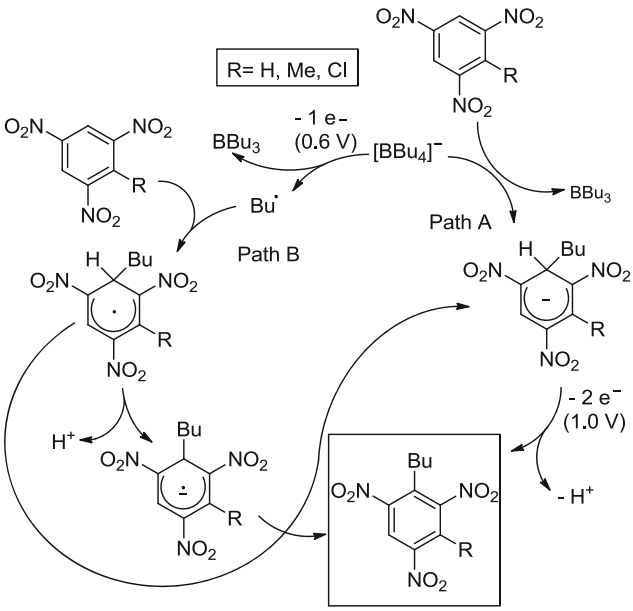
Scheme 11 Electrochemical synthesis of 1-butyl-2,4,6-trinitrobenzene

good yields [64]. Tetralkylborates react with 1,3,5-trinitrobenzene to form the corresponding σ^H-complexes [65].

The electrochemical approach for the alkylation of nitroarenes has also been demonstrated by the transformations of nitroaromatics by action of organometallic compounds RM (M = Li, MgX) (Scheme 10) [26] and tetraalkylborates (Scheme 11) [27].

Several types of σ-complexes are formed. σ^H-Complexes of arenes substituted in various positions of an aromatic ring have been established to react with the loss of two electrons and one proton (the S_N^H reaction), while σ^X-complexes (X = NO_2, Cl) undergo the departure of one electron and $X^{\cdot}$ (the S_N^X reaction). In the reactions of nitrobenzene and 1,3-dinitrobenzene (Table 3), yields of approximately 50% were achieved for monosubstituted arenes, and 10–50% for disubstituted products. Under the same reaction conditions 1,3,5-trinitrobenzene proved to undergo the S_N^X process with the loss of $NO_2^{\cdot}$.

Yields of products obtained by electrochemical methods are comparable with those reported in the literature for similar alkylations of aromatic compounds in the presence of chemical oxidants. In spite of experimental difficulties, we have succeeded to alkylate dinitrobenzene. The reaction has to be carried out in THF (highly resistant medium) because DMF undergoes decomposition in the presence of butyl lithium. Use of butyl lithium provides higher yields of the target alkylation products, than butylmagnesium chloride. Also equivalent amounts of reactants, nitroarenes and organometallic reagents, have been found to be essential to provide the best yields of the reaction products.

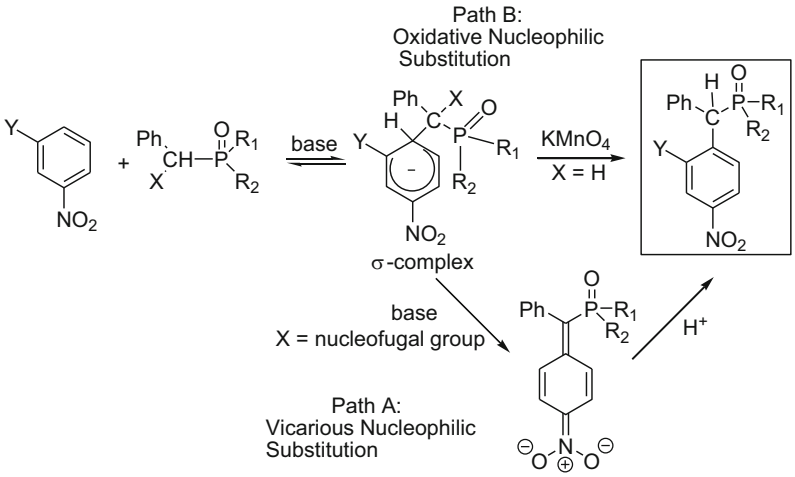


Scheme 12 General electrochemical mechanism for the synthesis of 1-butyl-2,4,6-trinitrobenzene derivatives. BBu_4^- acts as both nucleophile and reducing agent

The tetraalkylborate anion is a good alternative to organolithium or organomagnesium reagents to modify aromatic compounds through the nucleophilic aromatic substitution reactions. Indeed, 1,3,5-trinitrobenzene reacts with tetraalkylborates to form the corresponding σ^H-complexes (Scheme 11), followed by their oxidative transformations according to the S_N^H process (loss of the hydride ion).

1-Butyl-2,4,6-trinitrobenzene was obtained in 79% yield, in addition to dialkyl substituted 1,3,5-trinitrobenzene (14%) and recovered 1,3,5-trinitrobenzene (5%) (Table 3). Importance of the experimental part also has to be emphasized. To obtain the σ^H-complex of nitroarene with tetraalkylborate anion, you have to mix a solution of this anion (taken in an excess) with a solution of nitroarene and to wait for 2 h followed by electrochemical oxidation of the σ^H-complex at 1.06 V.

Tetraalkylborate anion is oxidized into tetraalkylborate radical at 0.60 V (Scheme 12), which is then transformed into Bu· that can react with 1,3,5-trinitrobenzene. The resulting radical species eliminate a proton, thus giving the corresponding nitroaromatic radical-anion. The latter is oxidized by the cyclohexadienyl radical (according to the standard potentials of redox pairs) [38, 66]. This reaction is somewhat similar to the termination step in the $S_{RN}1$ aromatic substitution reactions [64, 67, 68]. When the electrolysis is carried out at 1.06 V, the σ^H-complexes are oxidized (path A, Scheme 12), as well as tetraalkylborate anions (path B, Scheme 12). The generation of Bu· allows to improve yields of the S_N^H products, but Bu· can also attack the S_N^H product to form dialkyl trinitrobenzene. This process appears to be more important at the final stage of the reaction, when



Scheme 13 Vicarious and oxidative nucleophilic substitutions of hydrogen in nitroarenes with phosphorous-containing reagents

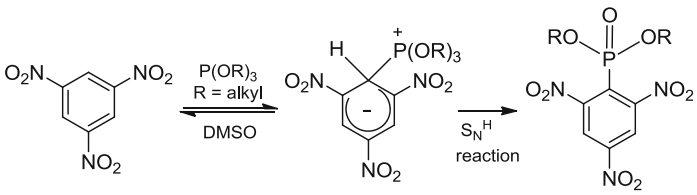
concentration of the monoalkyl arene is much higher than that of the starting nitroaromatic compound.

3.5 Phosphonylation Reactions. Phosphorous-Containing Compounds as Nucleophiles

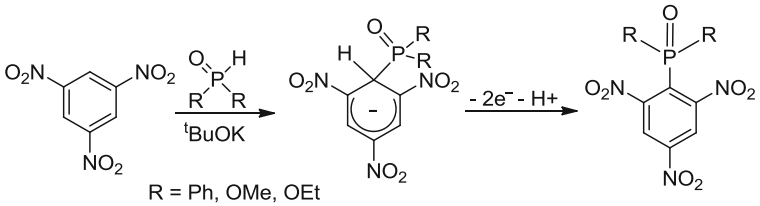
Nucleophilic aromatic substitution of hydrogen (S_N^H) or good leaving groups (S_N^X) by action of nucleophiles containing phosphorous is limited to a few examples of synthetic studies aimed at obtaining of aryl substituted phosphonic acids (in particular, for medicinal applications [69]), through either oxidative or vicarious displacement of hydrogen [70, 71]. In these S_N^H processes a new C–C bond is formed instead of C–P, when dialkylbenzyl phosphonates are used as nucleophiles in the presence of an external base (Scheme 13). The final S_N^H product can be obtained from the intermediate σ^H-complex by the action of the second equivalent of a base, which promotes the β-elimination of HX (vicarious S_N^H reaction, path A), or by using chemical oxidants such as potassium permanganate (oxidative S_N^H reaction, path B) [72].

The mechanistic study of the reaction of 1,3,5-trinitrobenzene with $P(OAlk)_3$ in DMSO has shown that picryl phosphonate, as the main S_N^H product, is formed through the intermediacy of the zwitterionic complex (Scheme 14) [59, 73–75].

The electrochemical method [28] was used to obtain nitroaromatic organophosphorus compounds by reacting 1,3.5-trinitrobenzene with dimethyl or diethyl phosphonates, and oxo(diphenyl) phosphonate as nucleophiles, in the presence of the *t*-BuOK, as shown in Scheme 15.

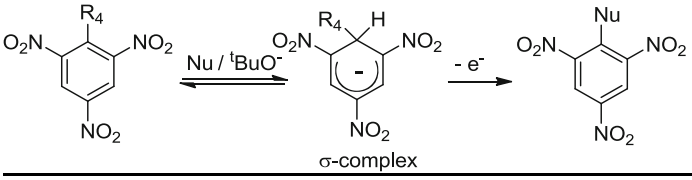


Scheme 14 The S_N^H reaction of trinitrobenzene with trialkylphosphites



Scheme 15 Electrochemical synthesis of dialkyl (2,4,6-trinitrophenyl)-phosphonates

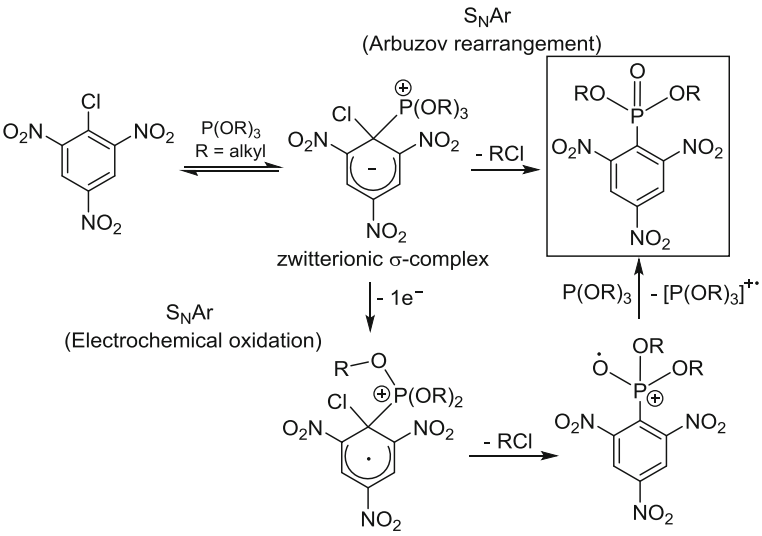
Table 4 Yields of products obtained by electrochemical oxidation of σ-complexes of nitroarenes with phosphorous-containing nucleophiles



R_4	Nu	Molar ratio[a]	σ (%)	$E_{pa}(\sigma)$[b] (V)	Substituion product[c,d] (%)[e]
H	$HPO(OMe_3)_2$	1:2:2	100	0.80	80
		1:1:1	90	0.88	70
	$HPO(OEt_3)_2$	1:1:1	81	0.86	33
	$HPOPh_2$	1:2:2	80	0.83	10
Cl	$P(OMe_3)_3$	1:50:0	100	–[f]	85
		1:5:0	100	1.07	100
	$P(OEt_3)_3$	1:50:0	100	–[f]	85
		1:5:0	100	1.07	93

[a]Molar ratio nitroarene (Ar): nucleophile (Nu): *t*-BuO^-
[b]All potentials are given vs. SCE reference electrode
[c]The S_N^H and S_N^X products were obtained by exhaustive electrolysis at E_{pa} + 0.1 V
[d]The oxidation products were analyzed by cyclic voltammetry, GC/MS and ^1H NMR
[e]This yield has been calculated on the basis of the σ-complex formed. The rest corresponds to recovered reactants
[f]Blank reactions, without oxidation

A typical S_N^H electrochemical process involves the formation of σ^H-complexes (yields 80–100%), and their electrochemical oxidation (the loss of two electrons and a proton) in all cases leads to the S_N^H substitution products, obtained in yields ranging between 10 and 80% (Table 4).



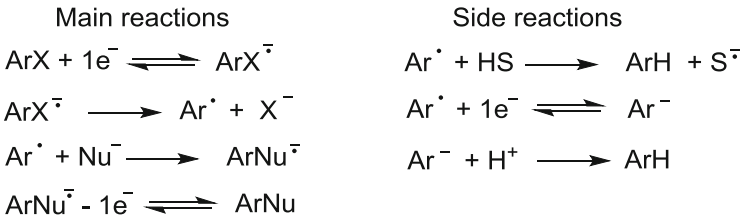
Scheme 16 Electrochemical synthesis of dialkyl(2,4,6-trinitrophenyl) phosphonate with $P(OR)_3$ as nucleophiles without external base

The reaction of 1,3,5-trinitrobenzene with trimethyl or triethyl phosphites as nucleophiles has been shown to give the S_N^H products in moderate yields (60%). On the other hand, good yields of the S_N^X products (85–100%) have been obtained by the reaction of 1-chloro-2,4,6-trinitrobenzene with the same nucleophiles (Table 4). Therefore, the S_N^X products can be obtained by means of either chemical reaction through the Arbuzov rearrangement, or by electrochemical oxidation of the intermediate zwitterionic complex (Scheme 16).

It is worth noting that no substitution products have been obtained in the reaction of 1,3,5-trinitrobenzene with PR_3 nucleophiles without any bases.

4 Electrochemically Induced S_N^X and S_N^H Reactions

Electrochemistry can also be used to induce aromatic nucleophilic substitutions by setting up the electrode potential at the level, which is appropriate to reduce an aromatic substrate. When this electrochemical process is carried out in the presence of a nucleophilic reagent, the S_N^X or S_N^H reactions take place. Indeed, halogenated derivatives of benzophenone, benzonitrile, and naphthalene undergo nucleophilic displacement reactions with thiolates, which are able to occur catalytically [76, 77]. The reaction mechanism involves the formation of the anion radical at the electrode and its further decomposition into a neutral radical, which reacts with a nucleophile, thus yielding the anion-radical of the substitution product. In case of the catalytic reaction, oxidation of the anion-radical species may occur by electron transfer with the substrate and/or the electrode (Scheme 17).



Scheme 17 Electrochemically promoted S_N^X reactions

The main competing reactions are the abstraction of H atom from the solvent of neutral radicals, and further reduction in radical species. Liquid ammonia was used as a solvent to avoid the transfer of H atom [78–80].

In both S_N^H and S_N^X reactions, which have so far been reported [22–28], the electrochemical activation appears to be involved in the reaction mechanism. The σ-complex is formed at the first step, and then it is oxidized electrochemically at the second step of the reaction.

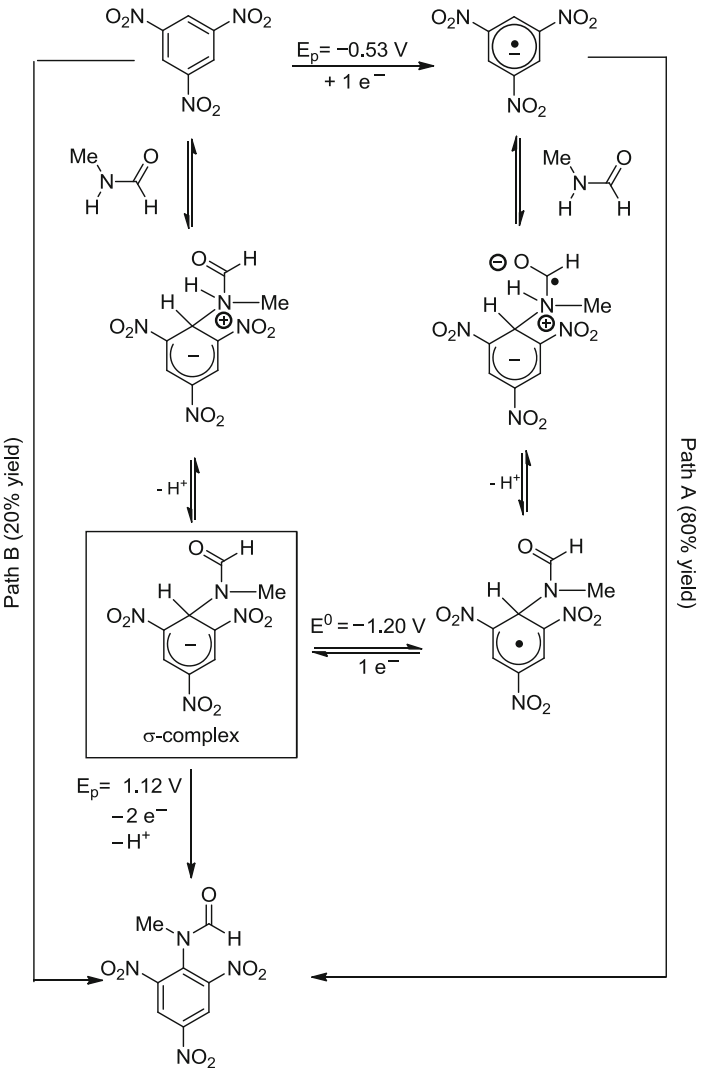
The formation of σ-complex seems to be a crucial step of the reaction between a nucleophile and an electron-deficient nitroarene. At the same time, there might be another strategy. By changing the electron character of substrate through the formation of radical-anions we generate electron rich species, which are able to react with neutral nucleophiles (electron poor). Thus, the choice of appropriate reactants for electrochemical reactions appears to be a crucial point. Indeed, 1,3,5-trinitrobenzene and N-methylformamide (nucleophile/solvent) proved to be suitable reactants [29].

Electrochemical study based on the combination of cyclic voltammetry and electrolysis at controlled-potential enabled the mechanistic aspects and synthetic scopes of the reaction to be established (Scheme 18).

A solution of 1,3,5-trinitrobenzene in N-methylformamide was subjected to electrolysis at −0.70 V (Path A, Scheme 18). The controlled-potential electrolysis was stopped after a passage of one electron per each molecule. The formed anion-radical species of 1,3,5-trinitrobenzene were allowed to react with N-methylformamide. Under the used experimental conditions the σ^H-complexes were the only species present in the reaction mixtures. Exhaustive oxidative controlled-potential electrolysis at 1.30 V gave *N*-methyl-*N*-(2,4,6-trinitrophenyl)formamide (S_N^H product) in good yield (80%). Without a preliminary reductive electrolysis (Path B, Scheme 18), the same type of σ^H-complexes proved to be formed, and after exhaustive oxidative controlled-potential electrolysis at 1.30 V, *N*-methyl-*N*-(2,4,6-trinitrophenyl)formamide (S_N^H product) was obtained in 20% yield.

Similar results were obtained by using 3,5-dinitrobenzonitrile, 1,3-dinitro-5-trifluoromethylbenzene, and 1,3-dinitronaphthalene as starting materials.

The anodic substitution reaction is another electrochemical approach to induce the S_N^X and S_N^H reactions. The term "anodic addition reaction" is used in the literature, since an anodic process is exploited for the initial electrochemical generation of radical-cation intermediates [81, 82]. Hence, anodic addition involves

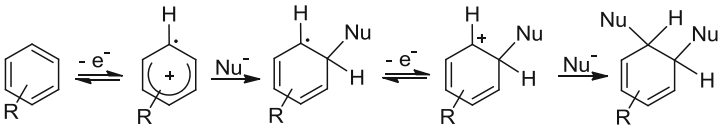


Scheme 18 Electrochemically promoted S_N^H process

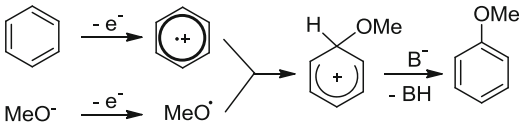
oxidation of an aromatic substrate ArH into the corresponding radical-cation, followed by the nucleophilic addition step (Scheme 19).

If oxidation of nucleophile takes place, the radical formed may react with an aromatic molecule (Scheme 20) [6, 82–84].

Use of the above-described anodic addition reactions enabled to perform hydroxylation of anthracene into 9,10-dihydroxianthracene in a good yield [85, 86], and also acetoxylation of 1,4-dimethoxybenzene into 2,5-dimethoxyphenylacetate in 51% yield [87].



Scheme 19 Anodic Addition. Formation of radical-cations from aromatic substrates



Scheme 20 Anodic Addition. Simultaneous formation of radical-cation from an aromatic substrate and a radical of nucleophile

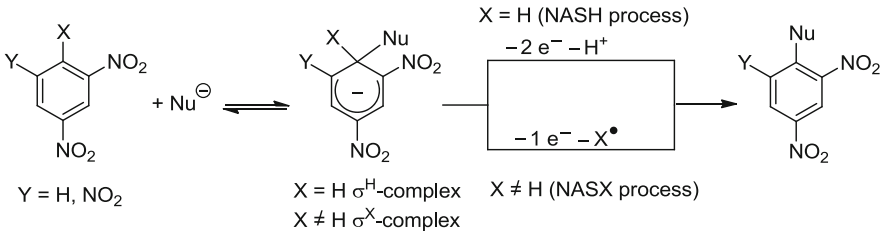
Recent studies demonstrate the achievements reached though anodic oxidation of catechols in the presence of α-oxoketene N,N-acetals [88, 89].

5 Thermodynamic Studies of σ–Complexes

The electrochemical methodology proved to be an excellent approach to obtain substitution products by oxidation of σ-complexes (Scheme 21). Electrochemistry can be exploited to oxidize σ^X-complexes, and this way involves the loss of an electron and a radical $X^{\cdot}$ ($S_N{}^X$ reaction), or can be used to oxidize σ^H-complexes, and the latter process involves the loss of two electrons and a proton ($S_N{}^H$ reaction). As indicated in the previous sections, the electrochemical method is especially promising in those $S_N{}^H$ reactions which are more difficult to be realized by means of conventional chemical procedures.

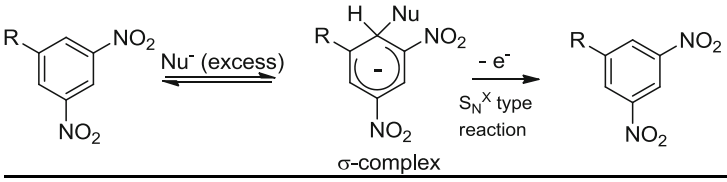
When anionic nucleophiles, such as $BH_4{}^-$, CN^-, CH_2COR^-, R^-, $BBu_4{}^-$, and ^-NHR (R is an alkyl group) are used, the $S_N{}^H$ products can be obtained in good yields through the typical $S_N{}^H$ process (with the loss of two electrons and a proton) [22, 24–27]. In the reactions of 1,3-dinitrobenzene and 1,3,5-trinitrobenzene with other nucleophiles, such as F^-, ^-OH, ^-OR, and ^-SR, the quantitative formation of σ^H-complexes is observed in all cases (Table 5). Following the electrochemical methodology, cyclic voltammetry, and controlled-potential electrolysis, these σ^H-complexes were oxidized at the corresponding potentials, and the starting nitroarenes were recovered in a vast majority of cases. Also, 1-fluoro-3,5-dinitrobenzene (2%), ethyl 3-nitrophenylether (14%), and ethyl 3,5-dinitrophenylether (31%) were obtained. These results indicate that the $S_N{}^H$ process is not realized properly, because yields of the $S_N{}^H$ products in all cases are below 31% (Scheme 22).

The results obtained indicate the complete formation of σ^H-complexes. However, the nature of nucleophiles is important for obtaining either $S_N{}^H$ or $S_N{}^X$ products, including recovery of the starting nitroaromatics. In other words, the



Scheme 21 Electrochemically promoted nucleophilic aromatic substitutions of hydrogen (S_N^H) or good leaving groups (S_N^X)

Table 5 Yields of products obtained by electrochemical oxidation of σ-complexes of nitroarenes with $^-$OH, $^-$OMe, $^-$SEt and F^-, as nucleophiles



R	Nu^-	$E_{pa}(\sigma)$[a] (V)	Final Product[b,c] (%)
H	$^-OCH_3$	0.72	100
	^-OH	0.59	100
	^-SEt	0.47	66[d]
	F^-	0.70	100
NO_2	$^-OCH_3$	1.18	100
	^-SEt	1.06	68[e]
	F^-	1.09	97[f]

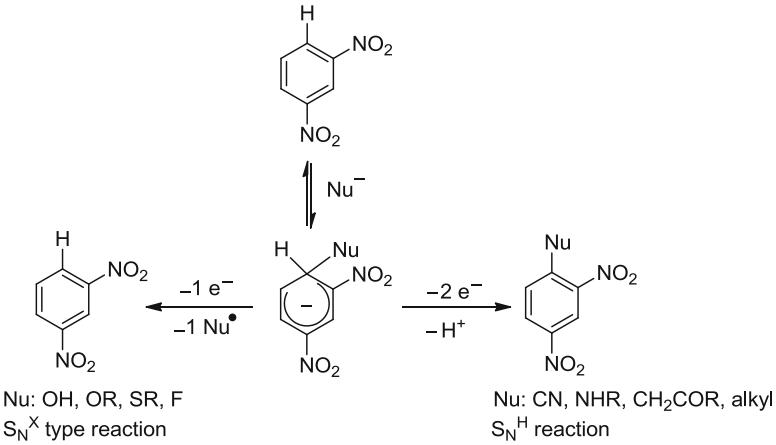
[a]All potentials are given vs. SCE reference electrode
[b]Products were obtained after exhaustive electrolysis at E_{pa} + 0.1 V
[c]The oxidation products were analyzed by cyclic voltammetry, GC/MS and ^{1}H NMR
[d]Ethyl 3-nitrophenylthioether (14%). The rest corresponds to recovered starting materials
[e]Ethyl 3,5-dinitrophenylthioether (31%)
[f]1-Fluoro-3,5-dinitrobenzene (2%)

difference between C–Nu and C–H bonds in dissociation energies has to be a decisive factor for the transformation of σ^H-complexes [30].

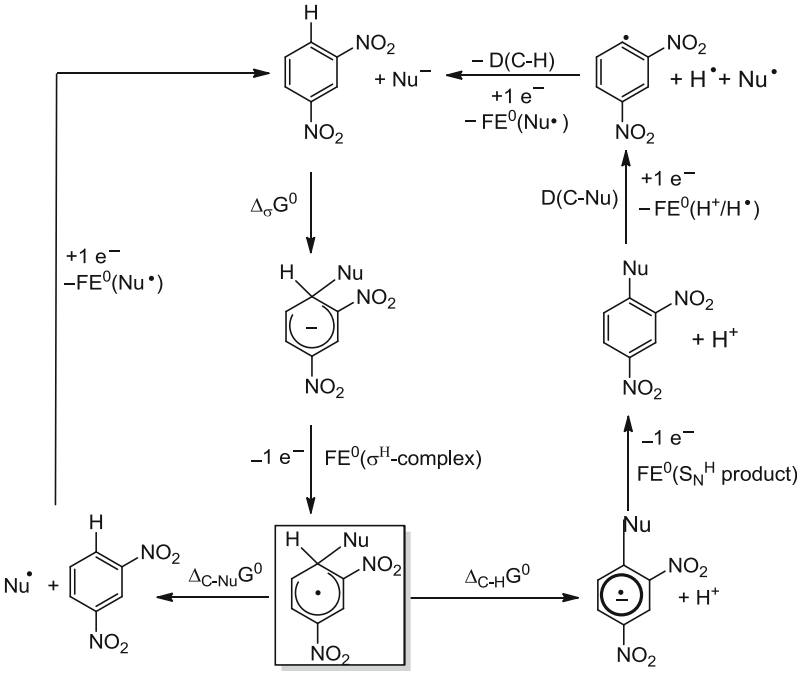
Thermodynamic cycles [90–93] can be used to relate the different energy patterns, such as the Gibbs standard chemical reaction energy ($\Delta_\sigma G^0$), the Gibbs standard electrochemical energy ($-FE^0$) for the transfer of one electron, and bond dissociation energy (Scheme 23).

The thermodynamic cycle begins with the formation of a chemical bond between a nitroarene and a nucleophile ($\Delta_\sigma G^0$) to give the σ^H-complex. The latter is oxidized at the second step with the removal of one electron [$FE^0_{(\sigma^H\text{-complex})}$].

The reaction determining step in Scheme 21 is the transformation of the radical derived from the σ^H-complex. It can undergo dissociation of either C–H ($\Delta_{C-H}G^0$) or C–Nu bond ($\Delta_{C-Nu}G^0$) to give radical-anion of the S_N^H product or the starting



Scheme 22 A plausible mechanism for the electrochemical oxidation of σ^H-complexes depending on the nature of nucleophiles



Scheme 23 Thermodynamic cycle for the S_N^H and S_N^X processes

dinitrobenzene, respectively. The radical-anion formed by cleavage of the C–H bond is oxidized into the S_N^H product (FE^0). The latter is transformed through homolytic dissociation of the C–Nu bond ($D_{C–Nu}$) into dinitrophenyl radical that

may be homolytically coupled with a hydrogen atom ($-D_{C-H}$). To close the cycle, protons are reduced to hydrogen atoms [$-FE^0_{(H^+/H^{\cdot})}$], and nucleophilic radical species $Nu^{\cdot}$ are transformed into Nu^- [$-FE^0_{(Nu^{\cdot}/Nu^-)}$]. The formation of dinitrobenzene is observed when the σ^H-complex radicals undergo dissociation of the C–Nu bond; reduction of $Nu^{\cdot}$ radicals to Nu^-($-FE^0_{(Nu^{\cdot}/Nu^-)}$) is only necessary to close the thermodynamic cycle.

The $\Delta_{C-H}G^0$ y $\Delta_{C-Nu}G^0$ values can be related, according to the thermodynamic cycle (Scheme 23), by Eqs. 1 and 2. The terms, such as $\Delta_\sigma G^0$, $E^0_{(Nu^{\cdot}/Nu^-)}$ [91–94] and $E^0_{(\sigma^H\text{-complex})}$ [83], which are difficult for experimental access, proved to appear in both equations. Fortunately, the difference between the two $\Delta_{C-H}G^0$ and $\Delta_{C-Nu}G^0$ values (Eq. 3) depends on bond dissociation energies and standard reaction potentials, $E^0_{(reaction)}$, and $E^0_{(H^+/H^{\cdot})}$. The bond dissociations were taken from publications [95–97], ignoring the entropic term (it has been accepted that it can be equal to 1 meV K^{-1}, which is equivalent to 0.02 kcal mol^{-1}) [98]. Values of standard potentials have been tabulated in the papers [22–27, 94, 99]. In order for the $S_N{}^H$ process to be a favorable relative to $S_N{}^X$, it is necessary that $\Delta_{C-H}G^0 < \Delta_{C-Nu}G^0$, Eq. 4. Equation 6 shows the bond dissociation energy, D_{C-Nu}, which is required for the $S_N{}^H$ reaction to be a favorable one.

On substituting the D_{C-H}, $E^0_{(reaction)}$ and $E^0_{(H^+/H^{\cdot})}$ values are 111.3 kcal mol^{-1}, −0.83 V and −1,53 V, respectively. In accordance with the above mentioned references, the D_{C-Nu} has to be higher than 95.2 kcal mol^{-1} (Eq. 7) in order for the $S_N{}^H$ process to be favorable.

Equations: **Thermodynamic Relationships**

$$\Delta_{C-H}G^0 = -\Delta_\sigma G^0 + D_{(C-H)} - D_{(C-Nu)} + \\ + FE^0_{(Nu^{\bullet}/Nu^-)} - FE^0_{(\sigma^H\text{-complex})} - FE^0_{(S_N{}^H\text{product})} + FE^0_{(H^+/H^{\bullet})} \quad (1)$$

$$\Delta_{C-Nu}G^0 = -\Delta_\sigma G^0 + FE^0_{(Nu^{\bullet}/Nu^-)} - FE^0_{(\sigma^H\text{-complex})} \quad (2)$$

$$\Delta_{C-H}G^0 - \Delta_{C-Nu}G^0 = D_{(C-H)} - D_{(C-Nu)} - FE^0_{(S_N{}^H\text{product})} + FE^0_{(H^+/H^{\bullet})} \quad (3)$$

$$\Delta_{C-H}G^0 < \Delta_{C-Nu}G^0 \quad (4)$$

$$\Delta_{C-H}G^0 - \Delta_{C-Nu}G^0 < 0 \quad (5)$$

$$D_{(C-H)} - FE^0_{(S_N{}^H\text{product})} + FE^0_{(H^+/H^{\bullet})} < D_{(C-Nu)} \quad (6)$$

$$95.2\,\text{kcal}\,\text{mol}^{-1} < D_{(C-Nu)} \quad (7)$$

Table 6 shows experimental values of D_{C-Nu} bond dissociation energies for various nucleophiles [95–97]. In accordance with the data of thermodynamic calculations, the complexes of nitroarenes with the $^-$OH, $^-$OR, $^-$SR nucleophiles have to undergo the $S_N{}^X$-type process, since their bond dissociation energies are lower than 95 kcal mol^{-1}.

Fluorinated compounds cannot be considered because the bond dissociation energies available in the literature for aromatic fluorinated compounds are varied

Table 6 Bond dissociation energies [86–88]

	C–SR	C–OR	C–OH	C–C	C–NHR
D_{C-Nu} (kcal mol^{-1})	61.7	76.0	82.0	101.8	103.2
	S_N^X type reaction			S_N^H reaction	

from 87 to 127 kcal mol^{-1}. Moreover, the standard potential for oxidation of the fluoride ion F^-, $E^0_{(F^{\cdot}/F^-)}$, is estimated to be between 2.59 and 2.62 V in DMF at 298 K.

Finally, thermodynamic study explains the operating mechanism (S_N^H or S_N^X) in terms of standard potentials, as well as BDE values by comparison of relative stabilities of the σ^H-complex radicals.

6 Electrochemical C–H Functionalization of Heteroarenes

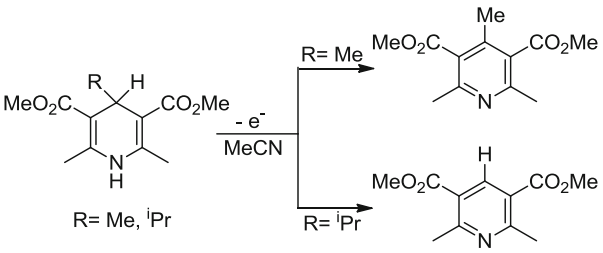
Anodic addition appears to be the main electrochemical method used for direct nucleophilic functionalization of C(sp^2)-bonds in heteroarenes. An excellent review summarizes all these studies [82]. Especially important area for the application of this methodology is preparative electrochemical oxidation of 4-alkyl-substituted 1,4-dihydropyridines (Scheme 24) [100]. Indeed, the electrolysis of 4-methyl substituted 1,4-dihydropyridine in acetonitrile in a divided cell on a platinum electrode at potential 1.2 V vs. SCE results in the formation of dimethyl 2,4,6-trimethylpyridin-3,5-dicarboxylate in 96% yield through cleavage of the C–H bond. Contrary to that, oxidation of 4-*iso*-propyl analogue of the same 1,4-dihydropyridine affords dimethyl 2,6-dimethylpyridin-3,5-dicarboxylate in 93% yield due to the elimination of the *iso*-propyl group from C-4 (cleavage of the C–C bond) (Scheme 24).

Preparative electrochemical transformations of 2,2′-bithiophene provide an original way to mono- and dipyridinyl substituted products, depending on the applied potentials (Scheme 25) [101].

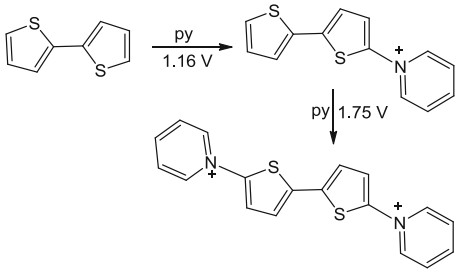
The S_NAr reactions of heteroarenes can be realized in a similar manner, as in the series of arenes [71, 82]. These nucleophilic reactions are analogous to electrochemical S_N^H transformations of arenes [22, 24, 25]. Terrier and co-workers considered an opportunity for electrochemical methoxylation of 4,6-dinitrobenzofuroxan by action of the methoxide ion via the S_NAr mechanism [21]. The intermediate σ^H-complex formed was oxidized successfully into the corresponding substitution product. Analogously, the formation of heteroaromatic amines has been suggested to occur via intermediacy of the corresponding amino adducts, as exemplified by the oxidation of the σ^H-complex derived from the reaction of pyrimidine with NH_2^- (Scheme 26) [3, 102–104].

Using the electrochemical methodology, we have performed cyanation of 2-nitrothiophene [22], aminations of 5-nitrothiophene-2-carbonitrile and 2-chloro-2-nitropyridine [24], and C-arylation of ketones with 2-chloro-2-nitropyridine [25] (Scheme 27).

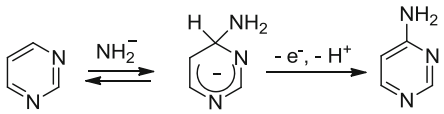
Scheme 24 Products derived from oxidation of 1,4-dihydropyridines in MeCN



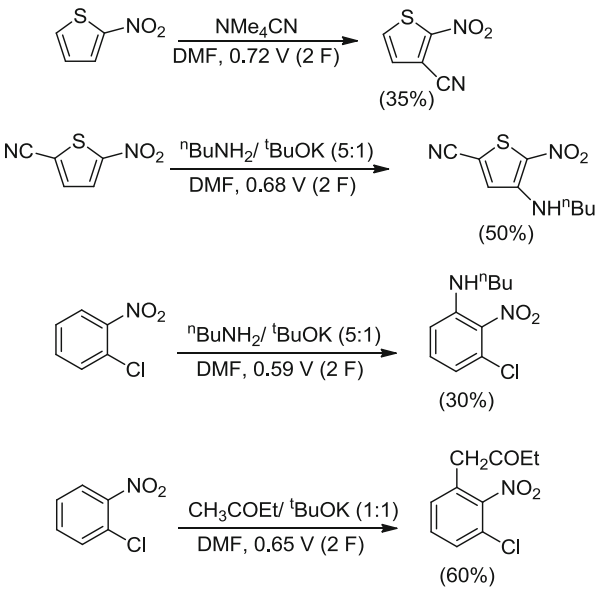
Scheme 25 Products derived from the anodic addition reactions of dithiophene in pyridine



Scheme 26 The S_N^H amination of pyrimidine



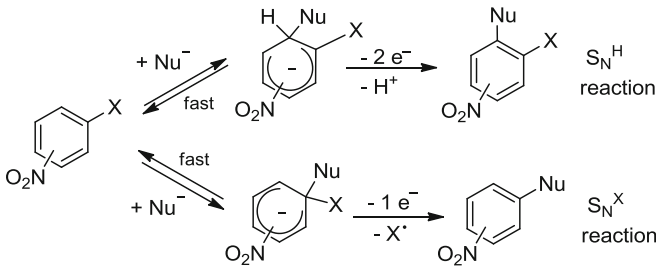
Scheme 27 Yields of products derived from electrochemical S_N^H reactions



The mechanism of these transformations is in agreement with that reported for the electrochemical S_N^H process (Schemes 5 and 19). All these reactions result in the formation of S_N^H products (yields are varied between 30 and 60%), and recover the starting aromatic compounds. The results are interesting enough to continue with a more extensive research on electrochemical S_N^H reactions of these heteroarenes.

7 Conclusion

The data in use for the electrochemical methodology in the chemistry of arenes and hetarenes allow to suggest the following general scheme for nucleophilic aromatic substitutions.



Electrochemical S_N^H and S_N^X reactions

According to this scheme the step 2 is realized by means of electrochemical oxidation of intermediate σ-complexes through the loss of one electron (S_N^X reaction) or two electrons (S_N^H reaction). These electrochemical oxidations proved to occur at different potentials (depending on the starting arene, nucleophile, and type of the intermediate σ-complex). It is worth to note that the oxidation peak potentials for σ^X-complexes are higher than those for the corresponding σ^H-complexes, and by using the correct potential one can obtain the "desired" substitution product.

In general, electrochemical C–H functionalization of arenes and heteroarenes has been developed, as a new synthetic route to structurally modified aromatics. A number of S_N^H transformations, such as cyanation, amination, C-arylation of ketones, alkylation, and phosphorylation have been performed by reacting arenes or heteroarenes with the cyanide ion, amines, ketones, RM and tetraalkylborate ions, and phosphorous compounds as nucleophiles, respectively.

In many cases electrochemistry proved to be a powerful tool to activate the S_NAr reactions. The cathodic reduction in aromatic compounds, prior to their interaction with nucleophilic reagents, is a new essential step of the S_NAr reactions. Moreover, a basic thermodynamic study explains (BDEs values of C–Nu vs. C–H), why F^-, ^-OH, ^-OR, and ^-SR nucleophiles do not react with arenes or heteroarenes.

In conclusion, it is worth to mention that several advantages of the electrochemical S_NAr reactions, such as a low cost and availability of reagents, atom economy, and high yields provide a good environmentally friendly basis for C–H functionalization of arenes and heteroarenes.

Finally, solvent is one of the important features of the S_NAr reactions. Changes in polarity of solvents, their protonation ability, electrical conductivity and other properties affect the nature of substitution products, as well as the time required to complete the reaction. The electrochemical method, which has first been used in classical organic solvents, should be extended to room temperature ionic liquids (RTILs). Recent results reported in the literature [105] show the feasibility of the S_N^H and S_N^X reactions in the $BMIM^+$ family of solvents. The mechanism and yields of substitution products are comparable with those obtained in the classic solvents.

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