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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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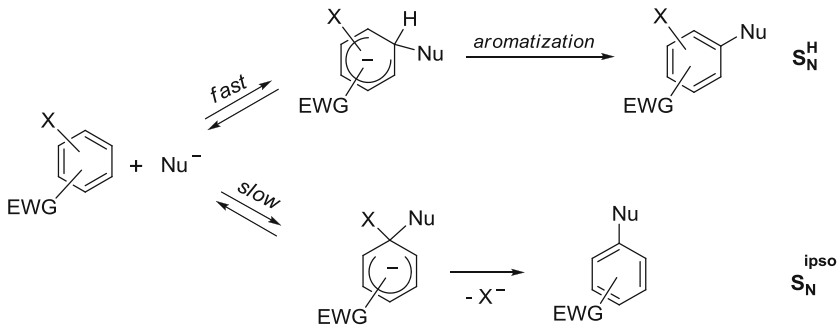
1 Introduction

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.

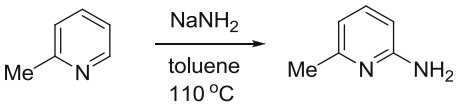
According to the accepted concept, reactions of electrophilic (het)arenes with nucleophiles usually proceed via the two-step "addition-elimination" mechanism (Scheme 1) (for a tutorial review, see [36]). At the first step, the formation of two types of intermediates, the σ^X- and σ^H-adducts, is considered 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.

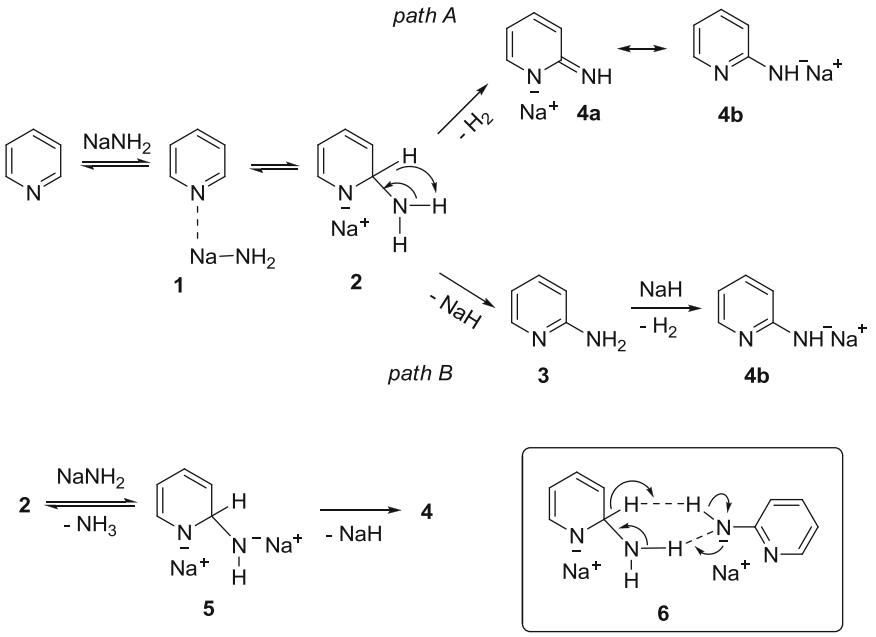
The present review surveys the data on the S_N^H-amination reactions of heteroaromatic substrates published mainly during the last decade. The S_N^H data accumulated in the literature are distributed into five sections, in accordance with the accepted mechanisms, operating in these S_N^H-amination reactions. 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**.

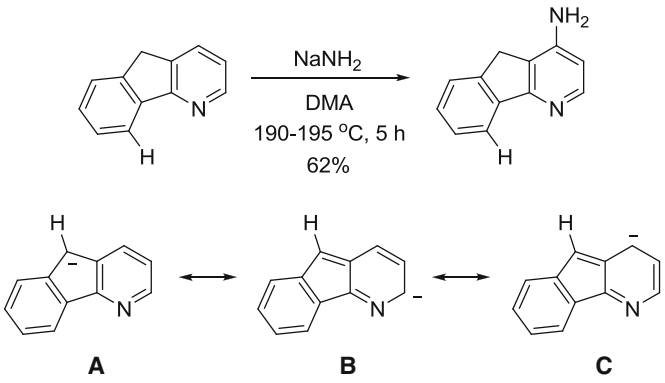
One more mechanism has been advanced, based on the fact that evolution of a considerable amount of ammonia gas takes place during the Chichibabin amination. Notably, this process becomes perceptible after some inductive period. Apparently, after accumulation of a certain amount of the adduct **2**, the 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.

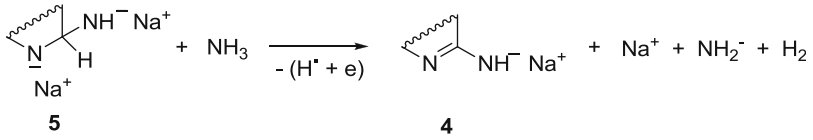
3 Oxidative Amination

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



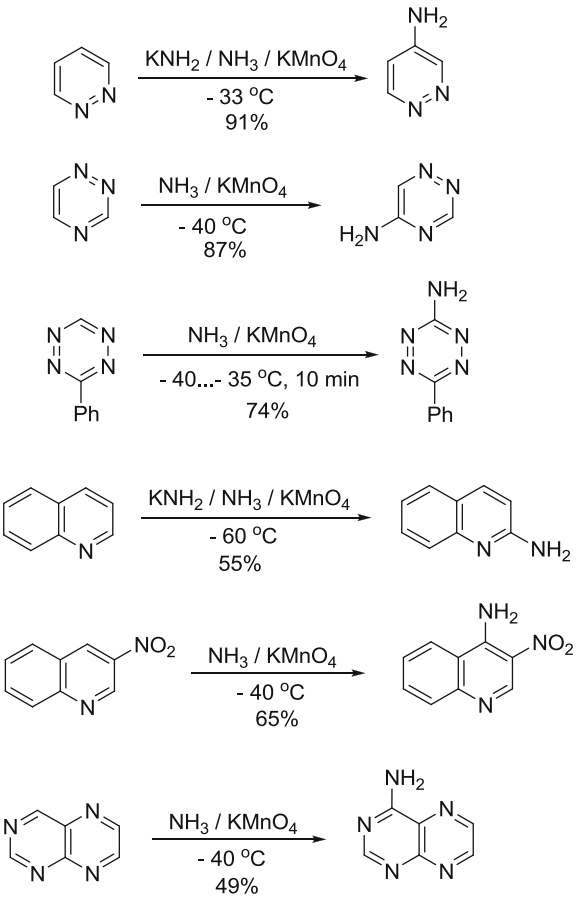
Scheme 5 Stepwise aromatization of the σ^H-adduct proposed by Bergstrøm

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.

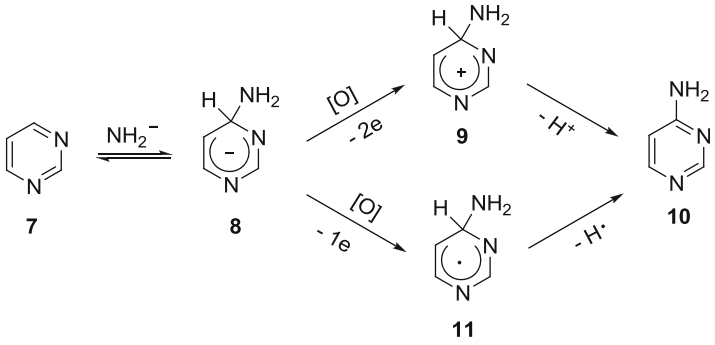
A major breakthrough in this field was achieved by Henk van der Plas with coworkers in early 1980s [12, 13, 49], when he had performed successfully a new version of the Chichibabin amination for the series of π-deficient azines in KNH_2/liq. NH_3 system, by using $KMnO_4$ as oxidant (Scheme 6). The reaction 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

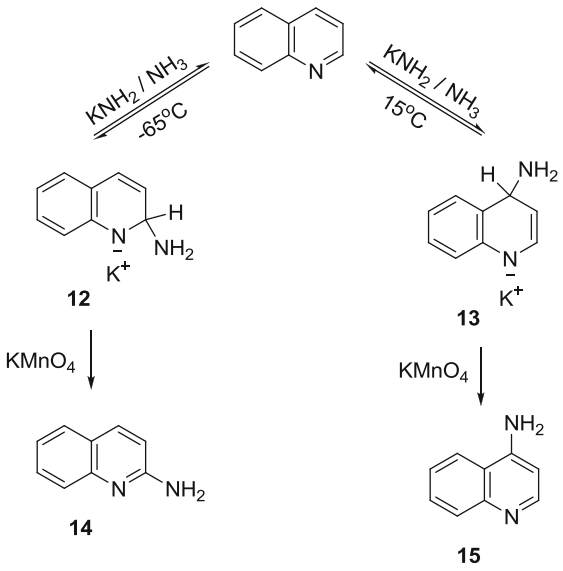


Scheme 6 Selected examples of oxidative amination reaction



Scheme 7 Proposed mechanisms for oxidative amination reaction

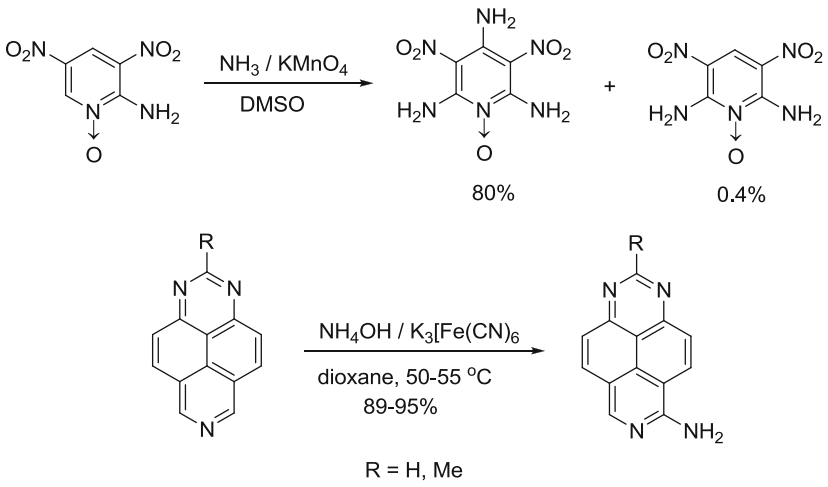
Scheme 8 Kinetic and thermodynamic control in oxidative amination of quinoline



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

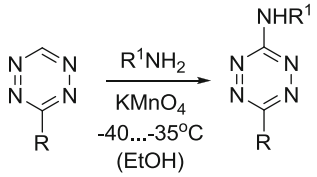
The aza group activation effect in the oxidative amination of azines is less than that of the nitro group. As an illustration: the reaction of 4-nitroquinoline and liquid ammonia in the presence of $KMnO_4$ produced 3-amino-4-nitroquinoline only in 86% yield [52]. Oxidative amination of 5-nitroquinoline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

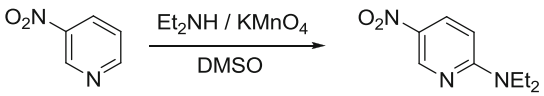
3.2 Alkylamination

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



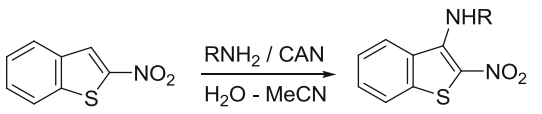
Scheme 11 Oxidative alkylamination of 3-nitropyridine in DMSO solution

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.

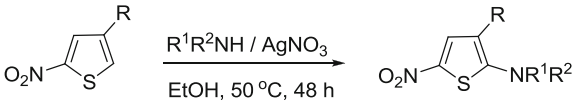
In order to improve the solubility of $KMnO_4$ in alkylamines, especially secondary ones, polar solvents were used. For instance, treatment of 3-nitropyridine with diethylamine and $KMnO_4$ in DMSO gave 6-diethylamino derivative in 60% yield, while without DMSO the reaction did not occur at all (Scheme 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

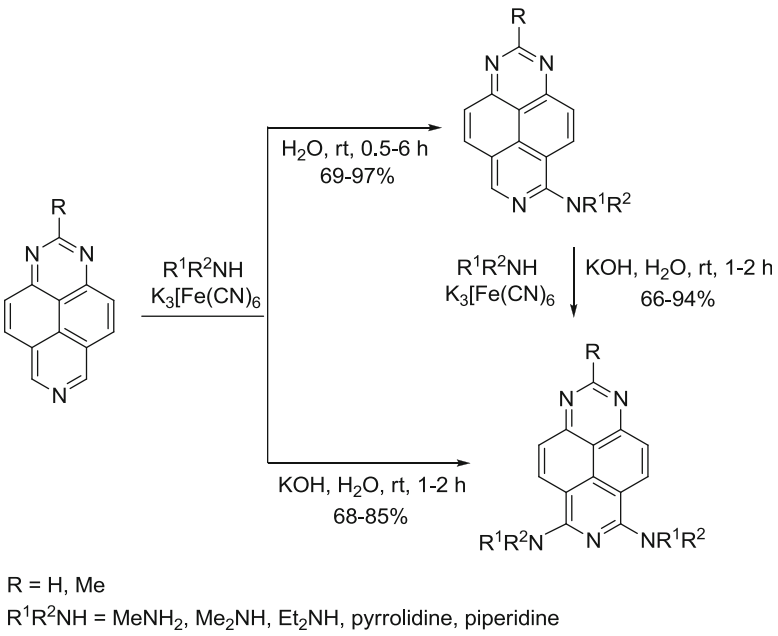
R^1R^2NH = Me_2NH, Et_2NH, $MePhCH_2NH$, pyrrolidine, morpholine, piperidine

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

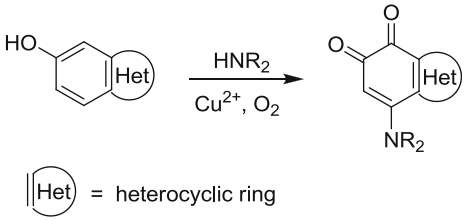
In contrast, alkylamination of 4-R-substituted 2-nitrothiophenes in the presence of silver nitrate proved to be possible only in cases of secondary amines (Scheme 13) [62]. Yields of 5-nitro derivatives formed as the sole product were ranged from 10 to 75%. It is noteworthy that oxidants other than $AgNO_3$,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



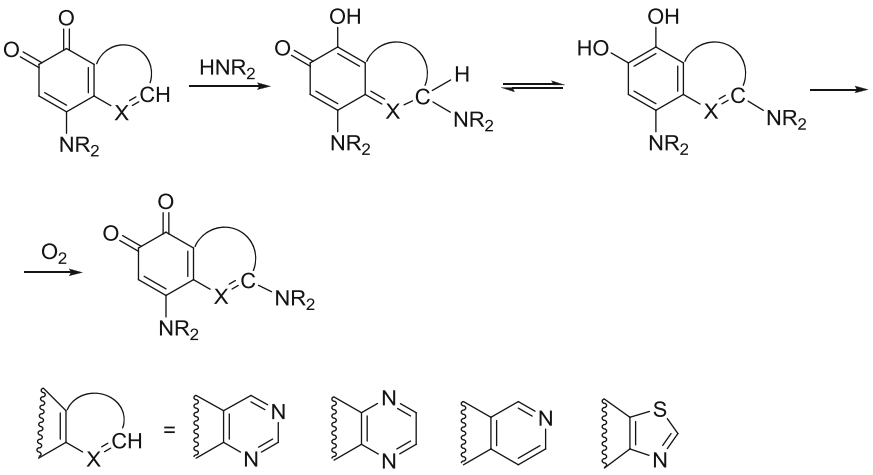
Scheme 14 Oxidative alkylamination of 1,3,7-triazapyrenes with $K_3Fe(CN)_6$



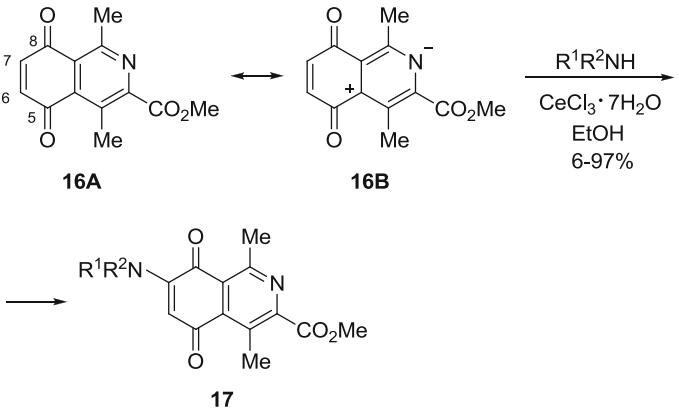
Scheme 15 Oxidative alkylamination of heterocyclic 1,2-quinones

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].



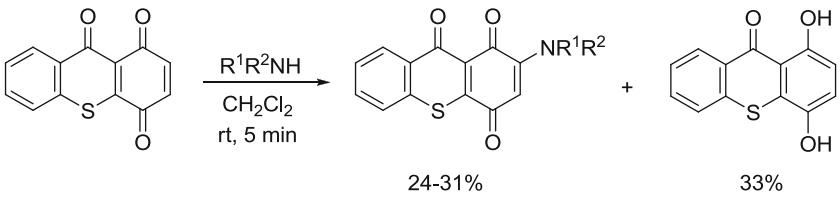
Scheme 16 Double oxidative alkylamination of heterocyclic *ortho*-quinones



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

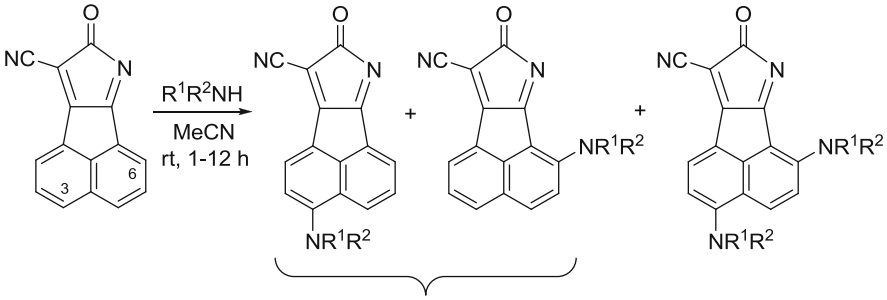
In some amination reactions the starting aromatic substrate itself can act as an acceptor of the hydride ion. For example, 1*H*-thioxanthene-1,4,9-trione reacts with alkylamines in CH_2Cl_2 (toluene or DMSO) to give the corresponding 2-amino compound in addition to 1,4-dihydroxy-9*H*-thioxanthen-9-one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

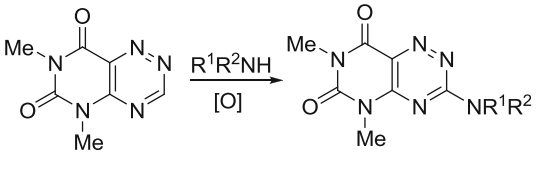


R^1R^2NH = *i*-$PrNH_2$, $BuNH_2$, $HOCH_2CH_2NH_2$, $H_2N(CH_2)_3CO_2Et$, $H_2N(CH_2)_2NEt_2$, piperidine, morpholine, thiomorpholine, N-methylpiperazine

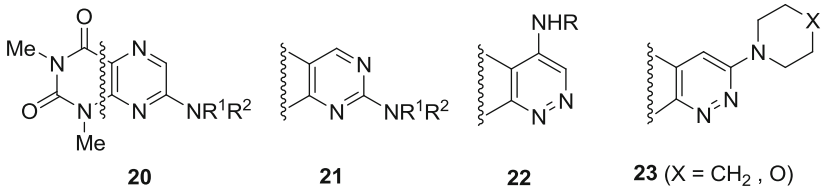
Scheme 19 Alkylamination of 8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrole-9-carbonitrile

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.

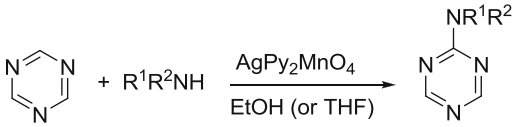
Perhaps, the best oxidant from those ever used in the alkylamination reactions in the series of azaaromatics is the complex of silver permanganate with pyridine $AgPy_2MnO_4$ (Py = pyridine). It is well soluble in alkylamines and can easily be prepared by mixing aqueous solutions of $KMnO_4$, pyridine, 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

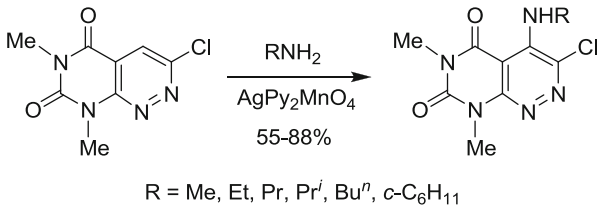


R^1R^2NH	%
NH_3	30
$MeNH_2$	26
i-$PrNH_2$	33
$BuNH_2$	56
n-$C_5H_{11}NH_2$	50
NH	39
O NH	63

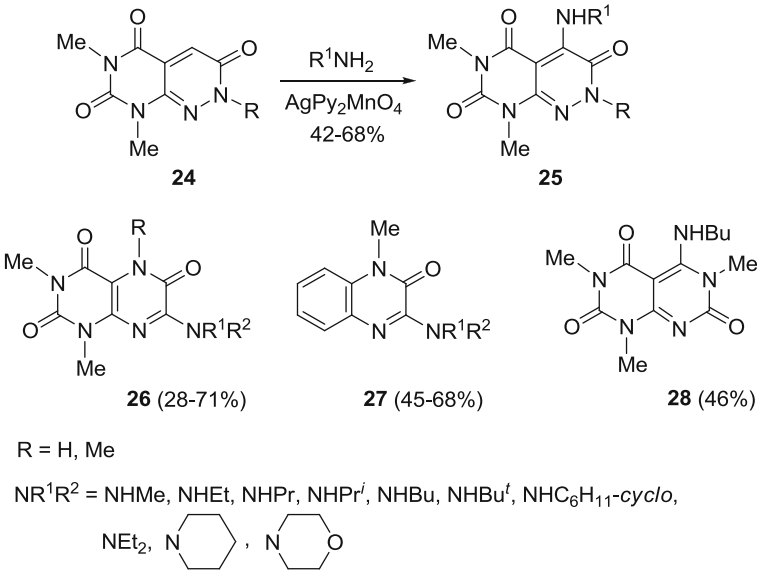
Scheme 21 Oxidative amination and alkylamination of 1,3,5-triazine

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 $KMnO_4$.



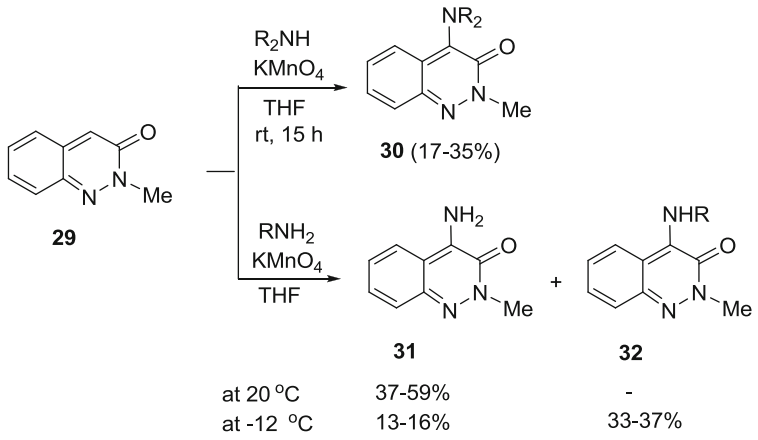
Scheme 22 Alkylamination of 3-chloro-6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione



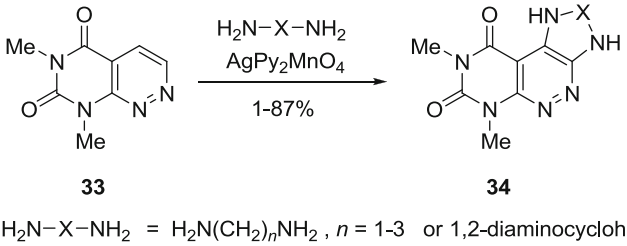
Scheme 23 Oxidative alkylamination of some condensed diazinones

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

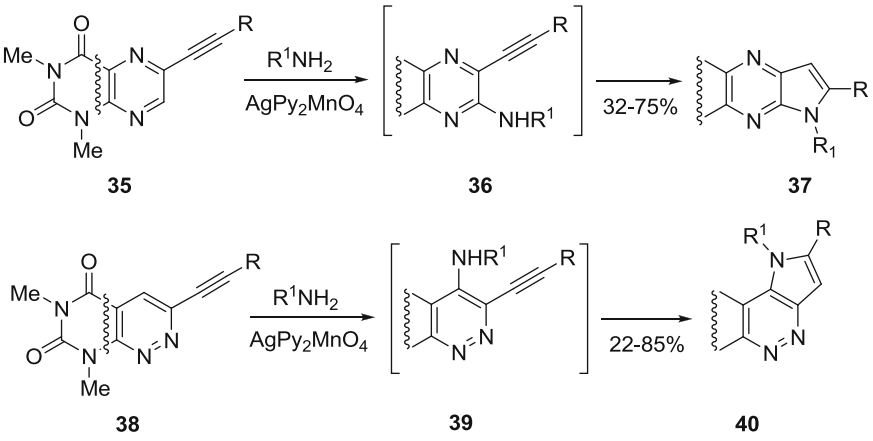


Scheme 25 Tandem oxidative alkylamination of pyrimidopyridazine substrate

(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].

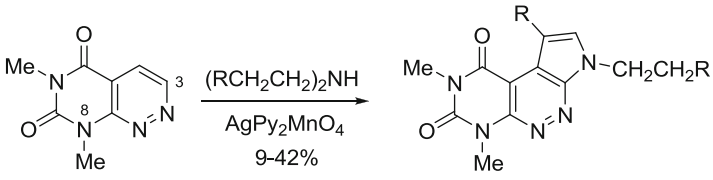
Recently, it has been demonstrated that involvement of oxidative alkylamination as a step into cascade transformations allows the synthesis of rather complicated compounds, which otherwise are hardly accessible. For instance, alkylamination of alkynyldiazines **35** and **38** in the presence of $AgPy_2MnO_4$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

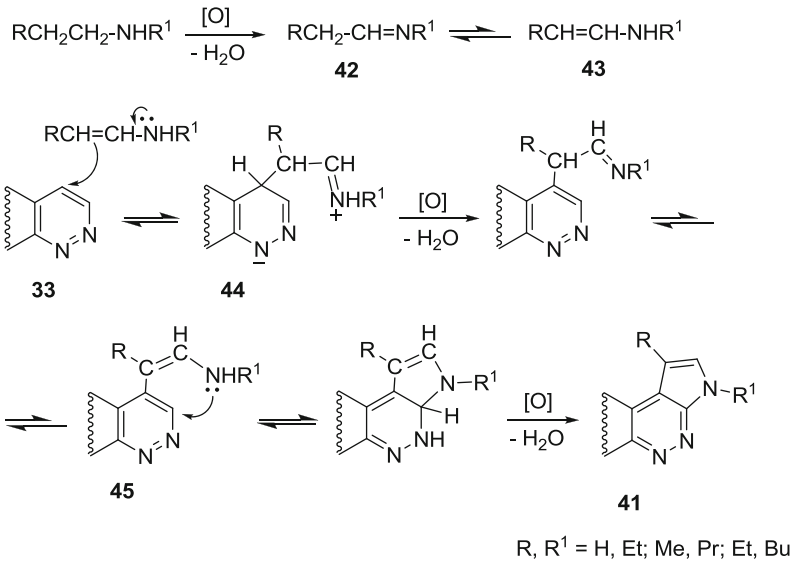


R = H, Me, Et

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].

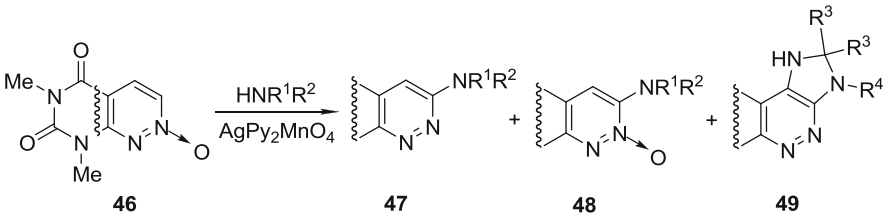


Scheme 28 Proposed mechanism for the cascade formation of pyrroles **41**

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].

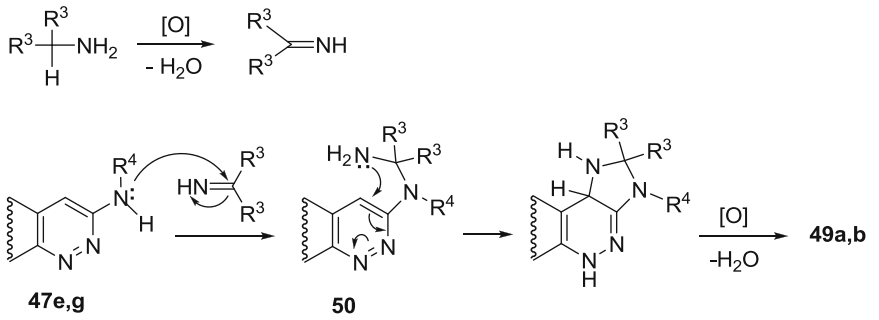
A plausible mechanism for annelation of the imidazoline ring includes the following steps (Scheme 30): (1) oxidation of cyclohexylamine (or isopropylamine) into the corresponding imine, (2) addition of 3-alkylaminopyridazine **47** to the imine C=N bond, which leads to the *gem*-diamine **50**, and (3) 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**)

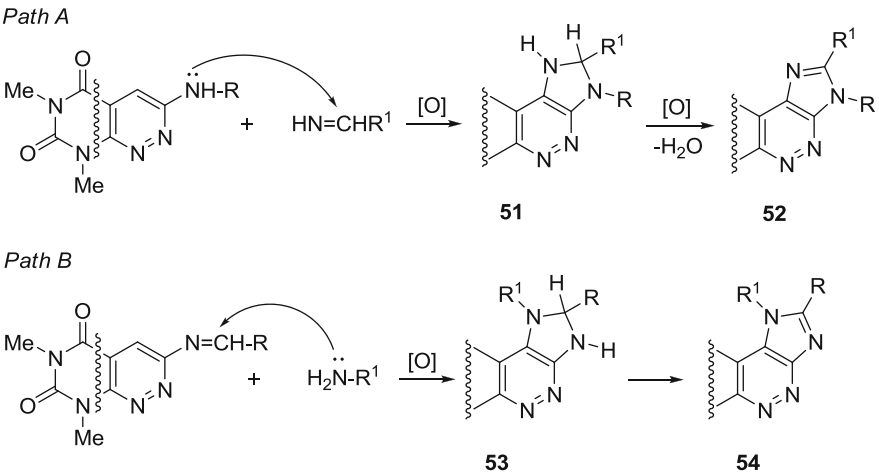
49: R^3, R^3 = -$(CH_2)_5$- , R^4 = *cyclo*-C_6H_{11} (**a**), R^3 = Me, R^4 = $CHMe_2$ (**b**)

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

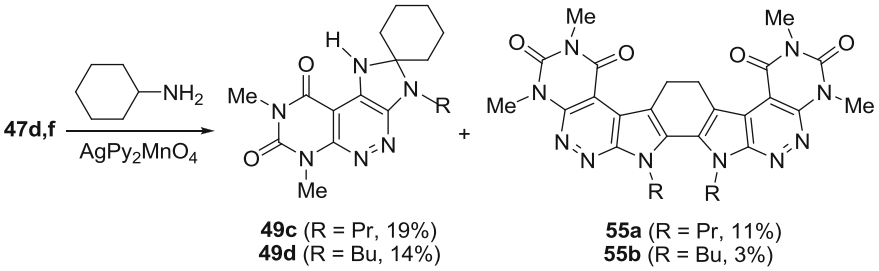
the oxidation of these amines and a relative stability of the corresponding imines. This mechanism was confirmed by the experiment, in which 3-cyclohexyl amino compound **47g** was allowed to react with cyclohexylamine and $AgPy_2MnO_4$ to give imidazoline **49a** in 65% yield.

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**



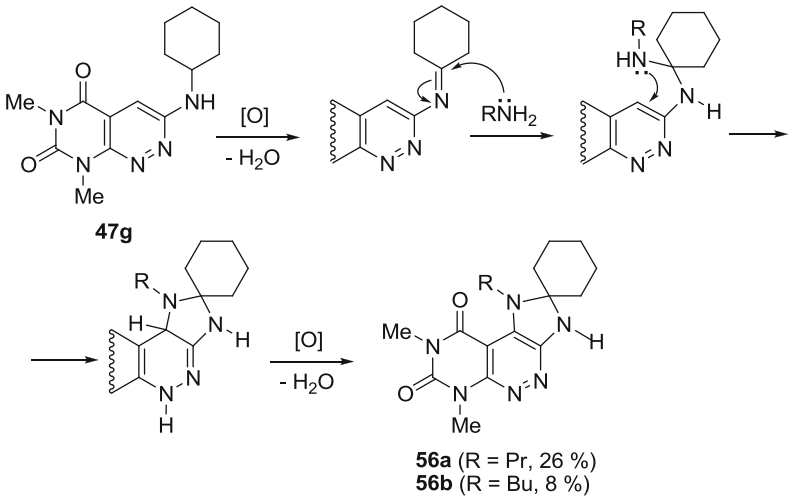
Scheme 32 Transformations of compounds **47d**,**f** in cyclohexylamine /$AgPy_2MnO_4$ system

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

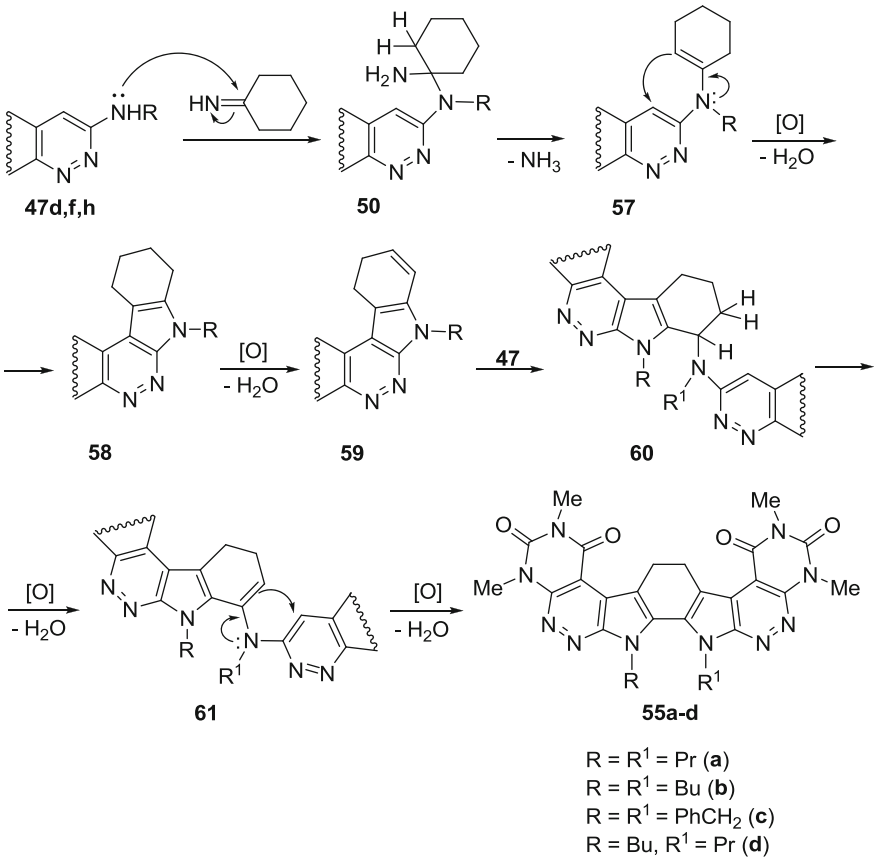


Scheme 33 Transformations of compound **47g** by action of $RNH_2/AgPy_2MnO_4$

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

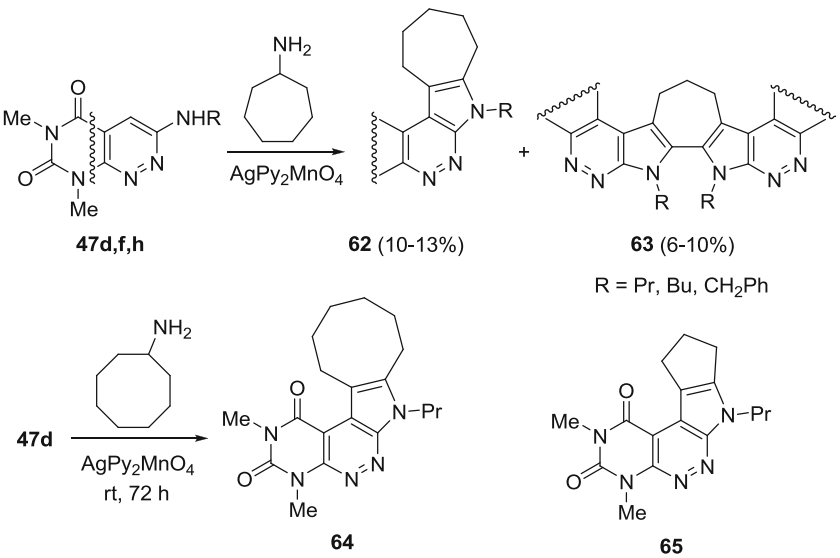


Scheme 34 A plausible mechanism for the formation of compounds **55**

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.

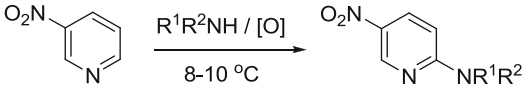
Thus, in the S_N^H-amination reactions an oxidant may take part not only in aromatization of the intermediate σ^H-adducts but also in chemical modification of nucleophile, substrate, and intermediates. This opens up new horizons for obtaining compounds, which are otherwise not easily accessible. In this 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



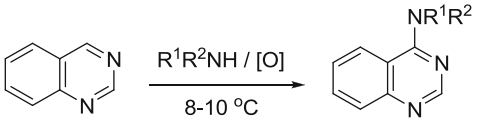
	Yields (%)			
Alkylamine	$KMnO_4$	$AgPy_2MnO_4$	$AgMnO_4$	CAN
i-$PrNH_2$	91	83[a]	–	22
$BuNH_2$	93	91[a]	–	–
n-$C_5H_{11}NH_2$	82	91[a]	–	–
$PhCH_2NH_2$	0	64[a]	–	–
Pyrrolidine	50	94	–	–
Piperidine	70	95	–	–
Morpholine	71	96	–	15
Homopiperidine	0	82	–	–
Et_2NH	0	14–20	9	–

[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 $TBACl/KMnO_4$.

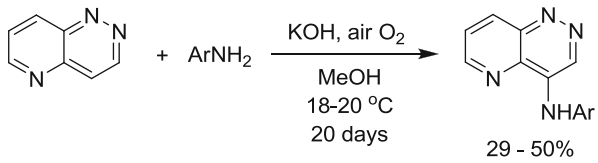
3.3 Arylamination

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].

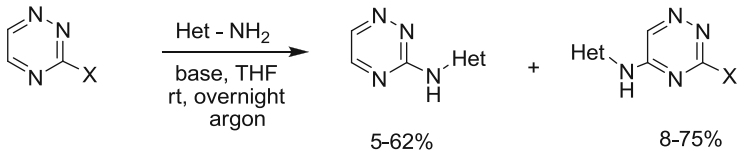
Contrary to that, hetarylamination of 3-X-1,2,4-triazines proceeds smoothly under inert atmosphere without external oxidant (Scheme 37) [90], although there are no doubts that it is the starting triazine, which plays the role of oxidant.

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

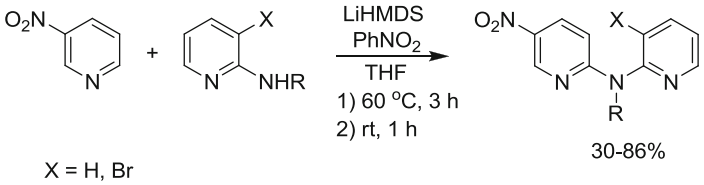


base: HTMP/*t*-BuOK/*n*-BuLi; HTMP/*t*-BuONa/*n*-BuLi

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

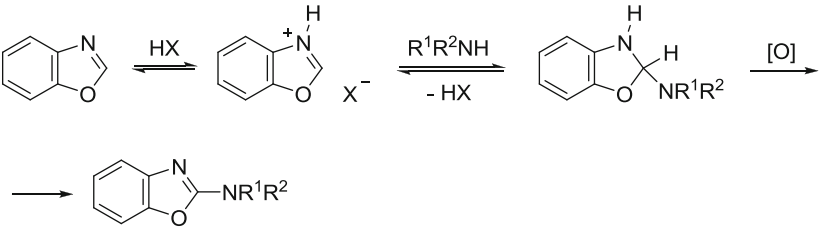
Unlike π-deficient azines and π-excessive heterocycles with the only pyrrole-like heteroatom, a number of azoles can be attributed to π-amphoteric systems. Indeed, it happens that a number of ring carbon atoms in an azole ring may carry partial positive charges, while others are negatively charged. Depending 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).

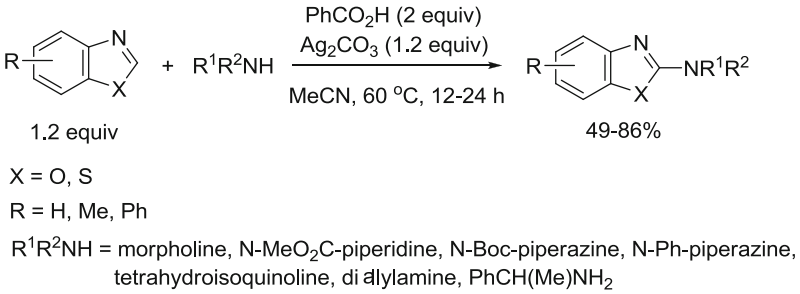
Indeed, benzoxazoles and benzothiazoles react smoothly with secondary and primary aliphatic amines in acetonitrile in the presence of benzoic acid and silver carbonate, thus giving rise to the corresponding 2-amino derivatives (Scheme 40) [94]. Also the reaction of 6-methylbenzothiazole with morpholine 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



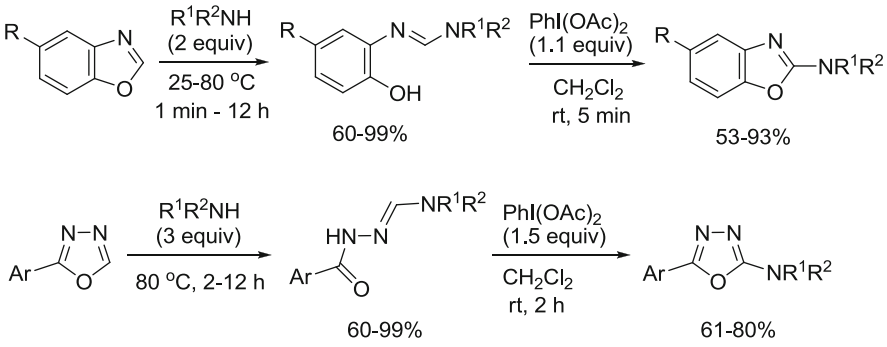
Scheme 40 Acid-promoted oxidative amination of benzoxazoles and benzothiazoles

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

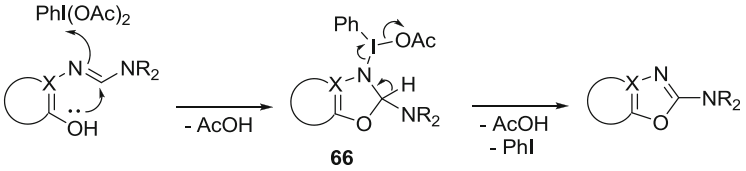
A metal-free protocol for amination of azoles has recently been reported [98]. It includes two steps: (1) the ring opening of benzoxazoles or oxadiazoles on heating with secondary aliphatic amines and (2) oxidative ring closure of the resulting amidines on their treatment with (diacetoxyiodo)benzene 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.

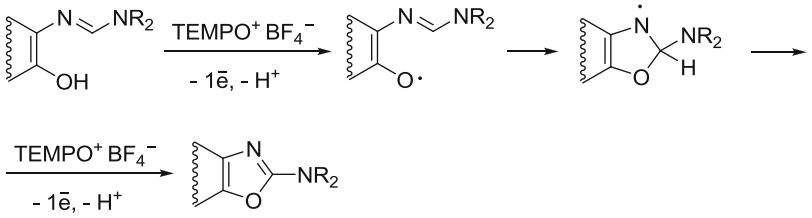
Amination of benzoxazoles and 1,3,4-oxadiazoles with secondary amines in the presence of Brønsted or Lewis acid and 2,2,6,6-tetramethylpiperidine-*N*-oxoammonium tetrafluoroborate ($TEMPO^+BF_4^-$) as oxidant has also been reported [99]. The reaction is supposed to proceed via the acyclic amidine intermediate,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



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



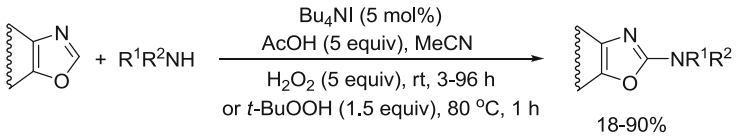
Scheme 42 Proposed mechanism for the ring closure step of the metal-free amination reaction



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

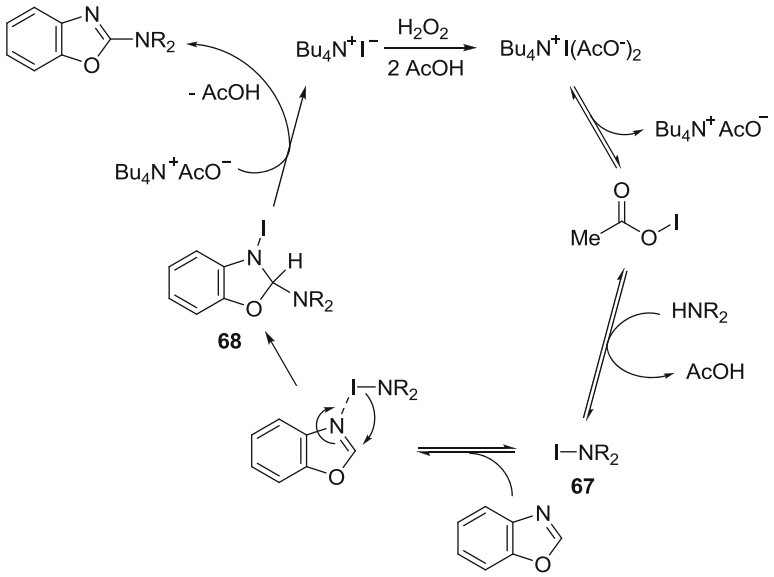
single-electron transfer mechanism (Scheme 43). It has been shown that conversion of amidines into aminoazoles can also be achieved with DDQ as oxidant.

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.*

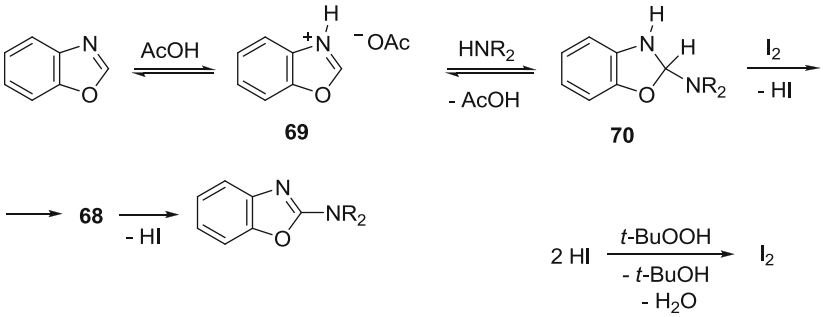
Scheme 44 Iodide-catalyzed oxidative amination of fused oxazoles



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.

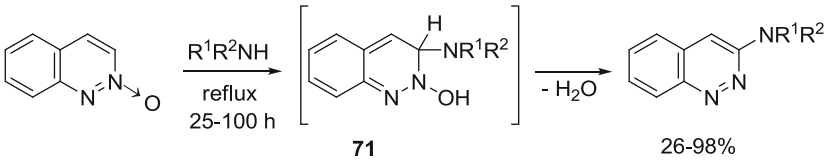


Scheme 46 Proposed mechanism for iodine-catalyzed amination of benzoxazoles

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

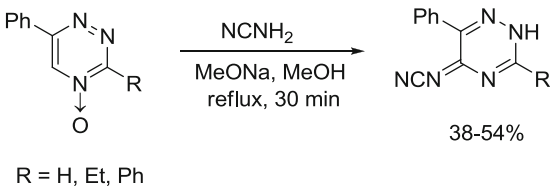
5.1 cine-*Amination*

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.

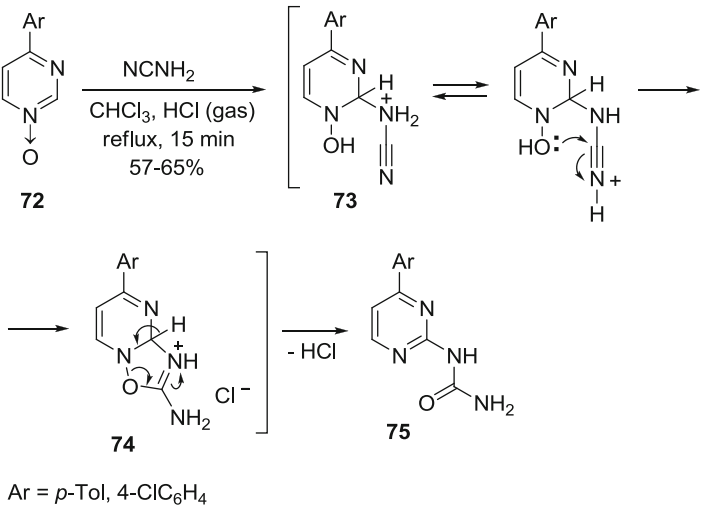
When treated with cyanamide in the presence of sodium methoxide 1,2,4-triazine 4-oxides are transformed into 5-cyanamino-1,2,4-triazines (Scheme 48) [106]. Presumably, these basic conditions are favorable for generation of more active nucleophilic species (via the equilibrium formation of $NCNH^-$ anions), 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.

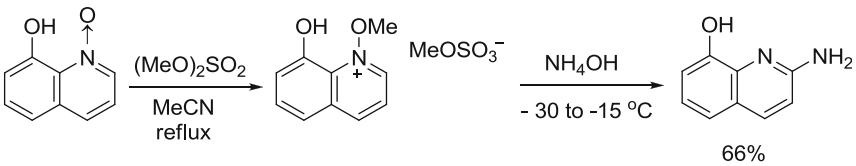
The presence of the N-oxide group in heterocyclic substrate opens another way for *auto*-aromatization of the σ^H-adducts. This is achieved via preliminary *O*-alkylation or *O*-acylation of the N-oxide group followed by addition of a nucleophile. Aromatization of the σ^H-adducts in these cases is based 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



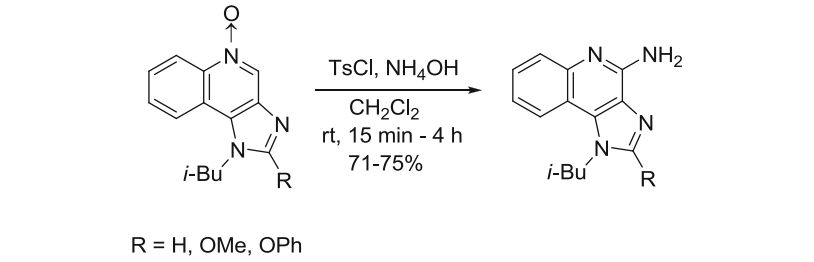
Scheme 49 Acid-catalyzed transformation of 4-arylpyrimidine-1-oxides by action of cyanamide



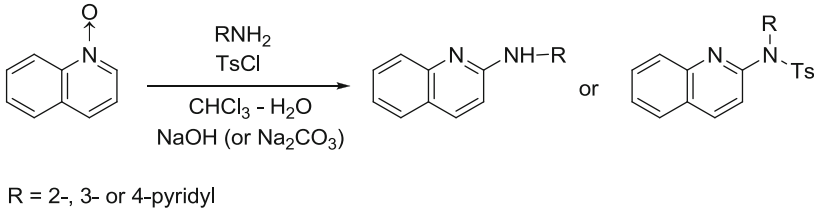
Scheme 50 *cine*-Amination of *N*-methoxy-8-hydroxyquinolinium salt

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

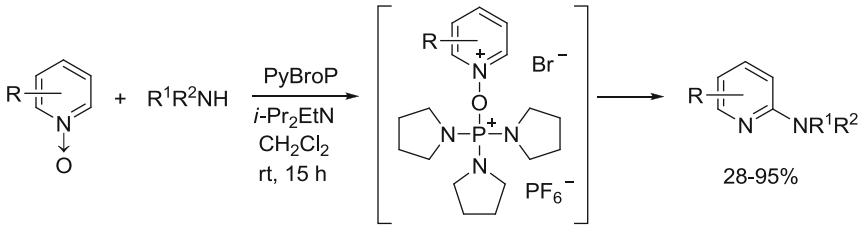


Scheme 52 *cine*-Amination of quinoline 1-oxide with aminopyridines

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).

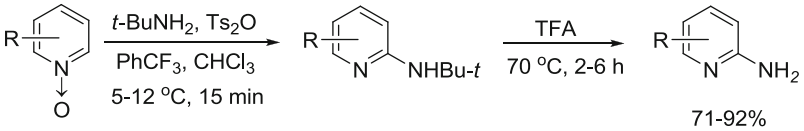


76

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

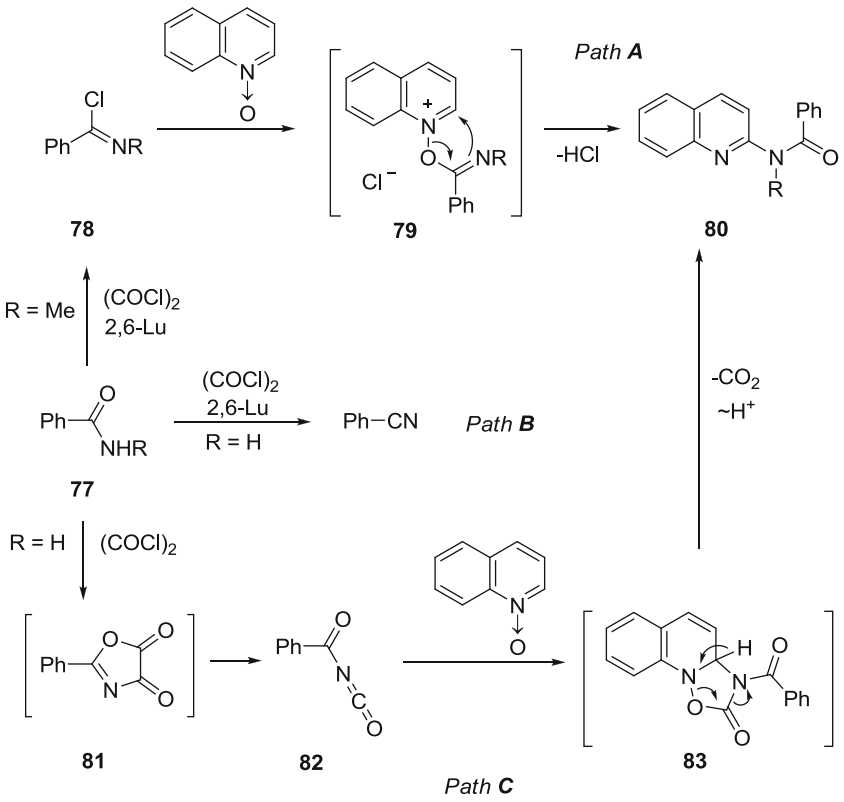
Scheme 54 Synthesis of 2-aminopyridines via *cine*-substitution reaction

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.

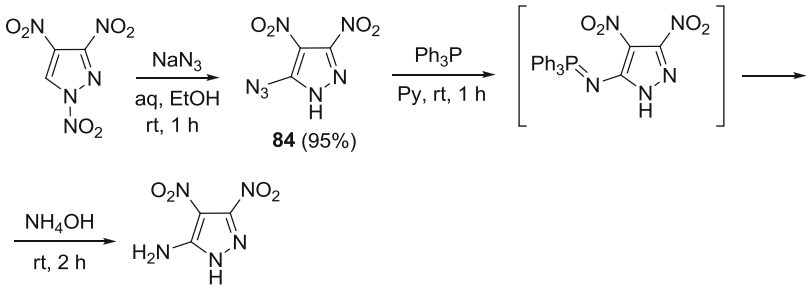
Saccharin, phthalimide, *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide, diethyl-*N*-(*tert*-butoxycarbonyl)phosphoramidate, and HMDS have recently been screened as ammonia surrogates in the amination of 3,5-disubstituted pyridine N-oxides activated by TsCl (*i*-Pr_2NEt, CH_2Cl_2, 0°C) [115]. Relatively 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%.



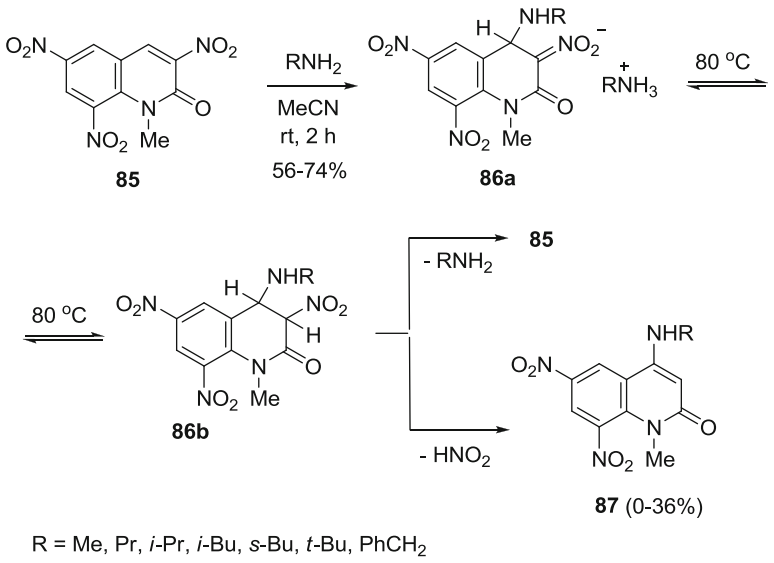
Scheme 56 Synthesis of 5-amino-3,4-dinitropyrazole

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].

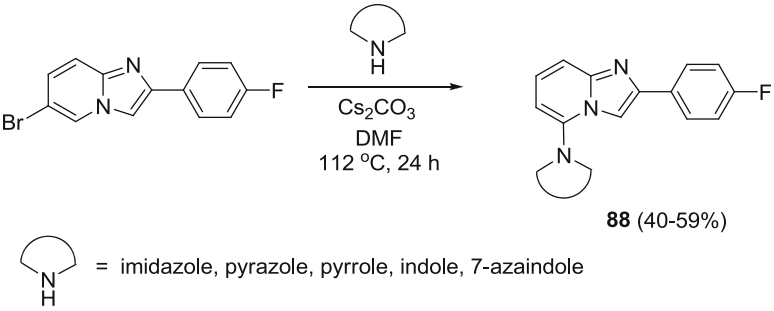
The *cine*-substitution reactions in *N*-fluoropyridinium salts with various nucleophiles, including *N*-nucleophiles, have been reviewed [121]. However, this approach did not find practical applications because of low yields of 2-substituted pyridines and the formation of complex mixtures of reaction 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.

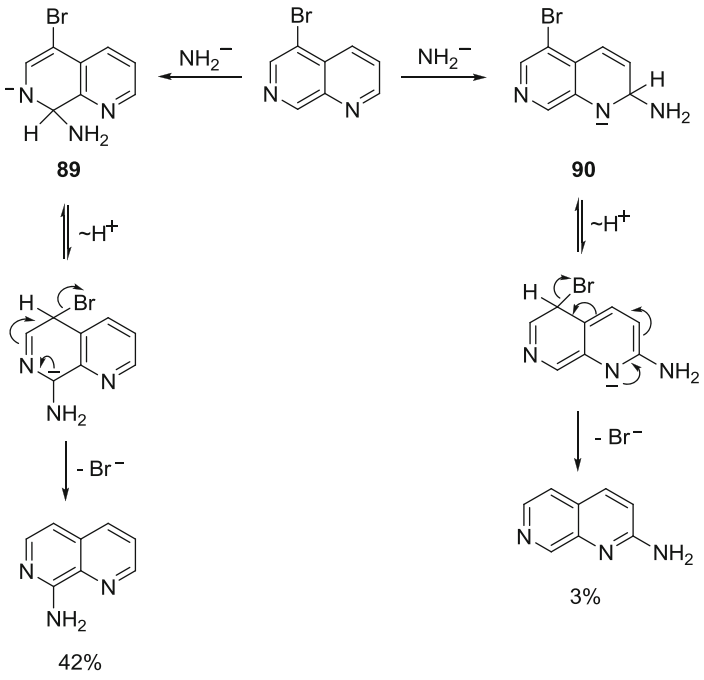


Scheme 57 *cine*-Amination of 1-methyl-3,6,8-trinitroquinolone



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].



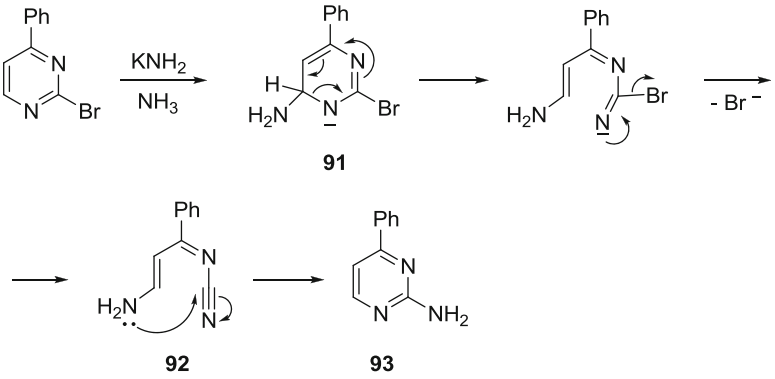
Scheme 59 An example of *tele*-amination reactions

5.2 tele-*Amination*

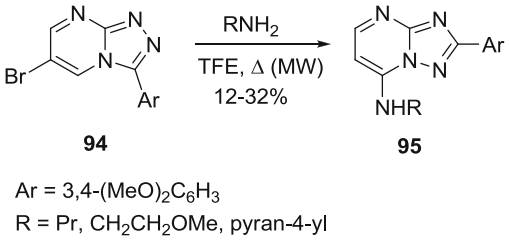
A good illustration of the *tele*-amination reactions is interaction of 5-bromo-1,7-naphthyridine with KNH_2 in liquid ammonia, leading to a mixture of 8-amino- and 2-amino-1,7-naphthyridines in 42 and 3% yields, respectively (Scheme 59) [126]. During the reaction the amide ion attacks C-2 and C-8 atoms, 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

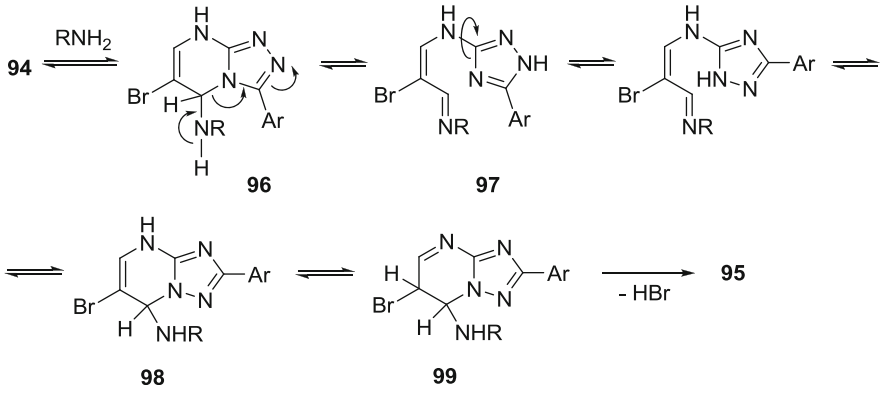
pyrimidine ring and elimination of the bromide ion. Then the open-chain intermediate **92** undergoes cyclization into aminopyrimidine **93**.

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].

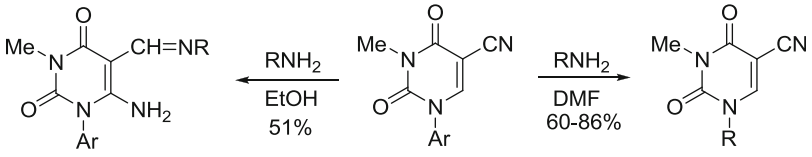
This transformation starts with the addition of amine to C-5 of **94** resulting in the formation of the σ^H-adduct **96** (Scheme 62). Subsequent opening of the pyrimidine ring, rotation around C(4)-N(exo) in the intermediate **97**, recyclization with participation of the triazole ring (**97**→**98**→**99**), 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.*

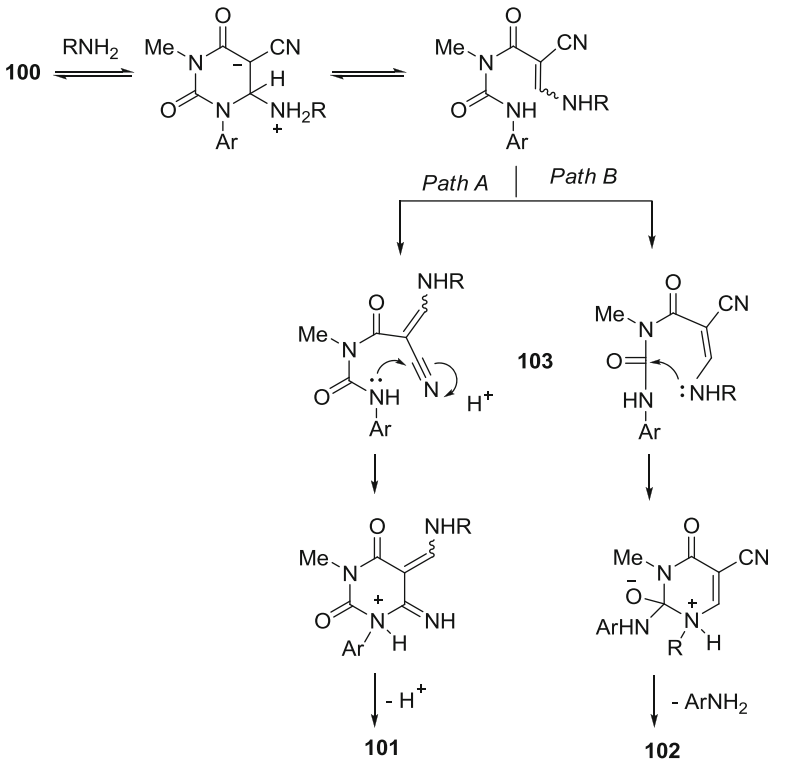
Scheme 63 Reactions of 5-cyanouracil **100** with alkylamines

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].

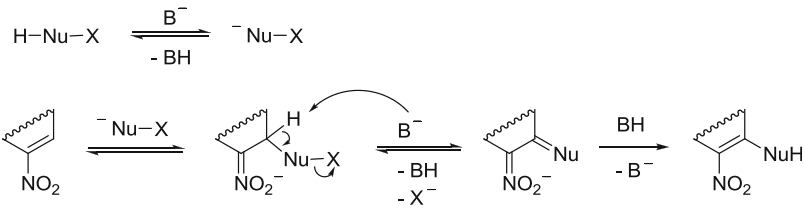
Also it should be noted that a very specific kind of the ANRORC transformations have been mentioned in the previous section, when discussing oxidative amination of benzoxazoles and 1,3,4-oxadiazoles (Sect. 4, Schemes 41 and 42).

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.

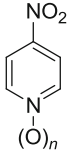
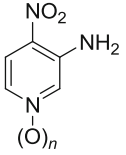
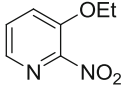
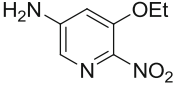
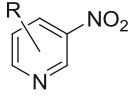
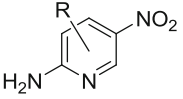
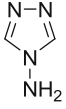
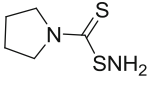
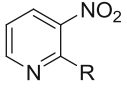
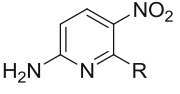
Recent examples of the VNS amination reactions in the series of six- and five-membered heterocycles and their benzo-fused analogues are summarized in Table 3. Nitro derivatives of pyridines, quinolines, isoquinolines, and quinoxalines proved to be especially suitable substrates. The reaction takes place 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.

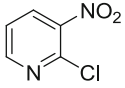
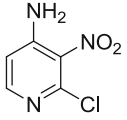
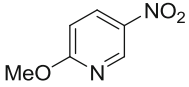
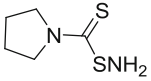
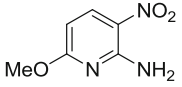
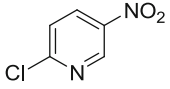
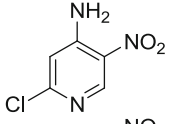
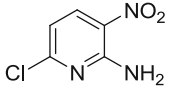
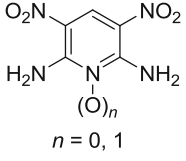
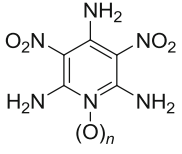
A rare example of the VNS-arylamination of 2-nitrothiophene by action of *N*,*S*-diphenylthiohydroxylamine as nucleophile has also been documented [136]. Unlike regioselective C(3)-amination of 2-nitrothiophene, the arylamination reaction affords a mixture of 3-phenylamino- and 5-phenylamino- derivatives in 1:3 ratio.

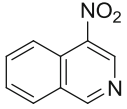
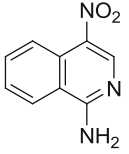
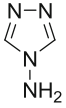
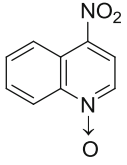
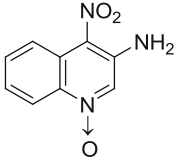
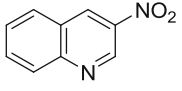
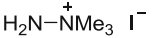
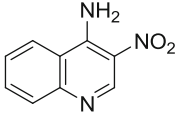
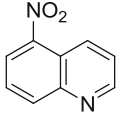
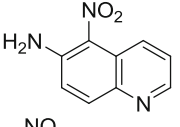
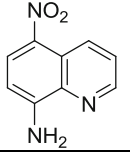
Table 3 Amination of six-membered heterocycles and their benzo-fused analogs via the vicarious nucleophilic substitution of hydrogen

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)

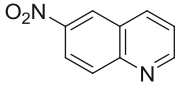
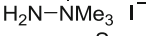
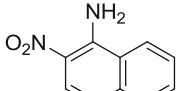
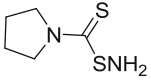
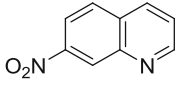
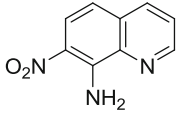
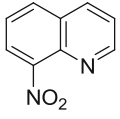
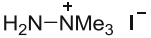
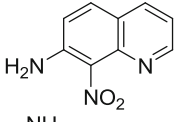
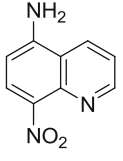
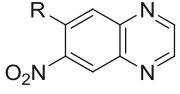
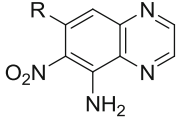
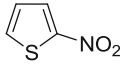
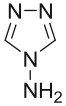
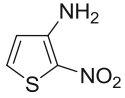
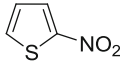
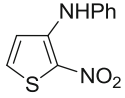
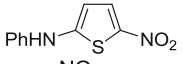
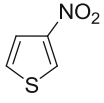
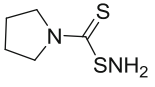
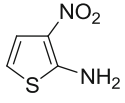
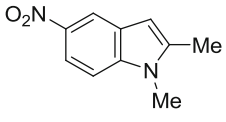
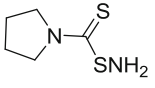
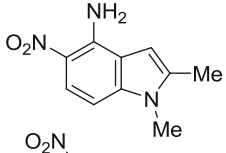
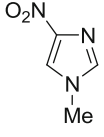
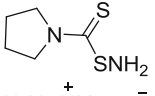
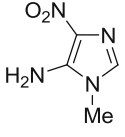
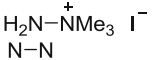
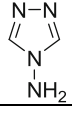
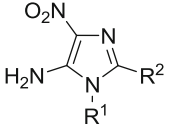
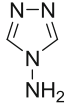
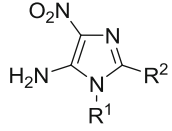
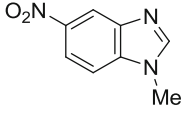
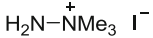
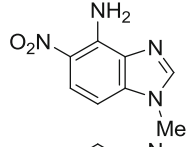
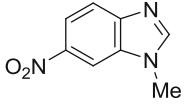
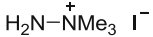
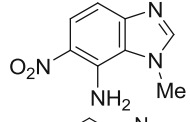
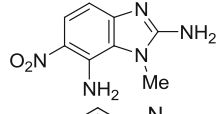
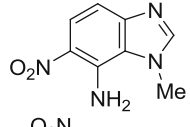
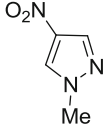
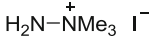
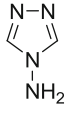
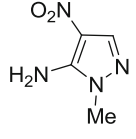
Substrate	Aminating agent	Reaction conditions	Products	Yield (%)	References
		*t*-BuOK, DMSO, rt, 1 h		95	[140, 141]
		*t*-BuOK, DMF, rt, 15 min		98	[136]
		*t*-BuOK, DMSO, rt, 2 h		92	[140, 141]
		*t*-BuOK, DMSO, rt, 4 h		68	[140, 141]
				18	
 R = H, F, Cl, Br	$NH_2OH{\cdot}HCl$	MeONa, MeOH, reflux, 1.5 h (or rt, 18 h)		27–56	[142]

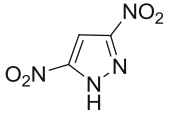
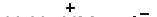
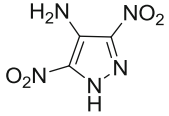
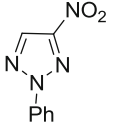
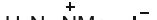
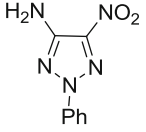
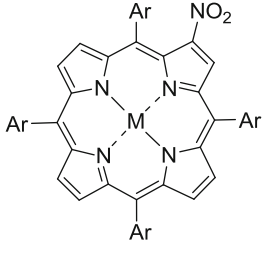
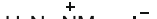
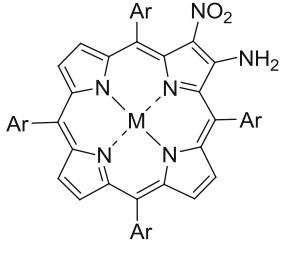
Table 4 Amination of five-membered heterocycles and their fused analogs via the vicarious nucleophilic substitution of hydrogen

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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