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Nucleophilic attack on the unsubstituted carbon atom of azines and nitroarenes as an efficient methodology for constructing heterocyclic systems

O N Chupakhin, D G Beresnev

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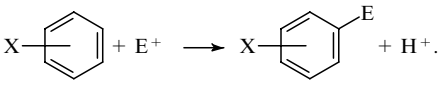
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Abstract. Data on new methods for the synthesis of fused azines by nucleophilic attack on the unsubstituted carbon atom of azines and nitroarenes are generalised. The review surveys tandem reactions of azines with binucleophiles comprising nucleophilic addition A_N-A_N, nucleophilic addition – substitution $A_N-S_N^{ipso}$, and nucleophilic substitutions $S_N^H-S_N^{ipso}$ and $S_N^H-S_N^H$. Intramolecular S_N^H reactions of azines and nitroarenes and other methods for the synthesis of fused heterocycles based on S_N^H nucleophilic substitution are also discussed. The bibliography includes 69 references.

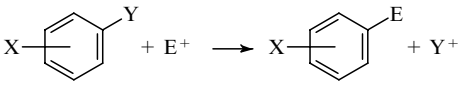
I. Introduction

The main procedures for the functionalisation of aromatic compounds involve electrophilic (S_EAr) and nucleophilic (S_NAr) substitution reactions. The S_EAr reactions, typical primarily of carbocyclic compounds, proceed predominantly as the electrophilic substitution of hydrogen. Strictly speaking, these transformations would be more correctly designated as S_E^HAr because less common reactions accompanied by the displacement of non-hydrogen groups (CO_2R, NO_2, NR_2, *etc.*) are conventionally symbolised by $S_E^{ipso}Ar$.

Transformation S_EAr (S_E^HAr):



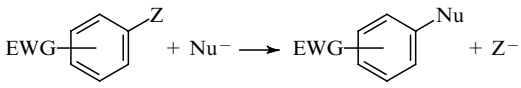
Transformation $S_E^{ipso}Ar$:



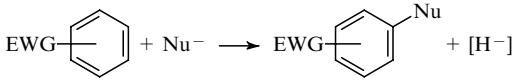
E is an electrophile.

Nucleophilic aromatic substitution reactions involve most often the *ipso*-substitution ($S_N^{ipso}Ar$) at the C_{Ar} atom bound to the Hal, N, O, P or S atoms.[1] Some S_NH reactions have long been used in industry (synthesis of nitrophenols, alizarin, 2-aminopyridine). The preparation of *p*-phenylenediamine from nitrobenzene and benzamide is currently one of the most advanced organic syntheses used in industrial processes.[2]

S_NAr ($S_N^{ipso}Ar$)



S_N^H (S_N^HAr)



Nu is a nucleophile; EWG is an electron-withdrawing group.

Presently, the S_N^{ipso} and S_N^H reactions and related processes are used as the main procedures for the modification of π-electron-deficient aromatic systems.[1,3] It should be noted that methods based on nucleophilic attack on the unsubstituted carbon atom of aromatic compounds have some advantages. Thus, the preliminary introduction of nucleofuges (Cl, NO_2, SO_3H, *etc.*) into the ring is not needed here and the hydride ion serves formally as the leaving group. In many reactions, water is removed from the reaction mixture as a by-product, which is of importance for the commercial use of these reactions in connection with increasing industrial requirements for environmental safety.

It should be noted that an aromatic substrate must be activated to be involved in the S_N^H processes. In reactions with arenes, this is most often achieved by the introduction of an electron-withdrawing substituent, for example, the nitro group, into the ring. In the reactions with heterocyclic compounds, the presence of the aza group is often quite sufficient. This group is comparable to NO_2 in its electron-withdrawing effect and also directs nucleophilic attack at positions 2 and 4.[1]

The present review surveys the data on the use of nucleophilic attack on the unsubstituted carbon atom of azines and nitroarenes for the construction of new heterocyclic systems.

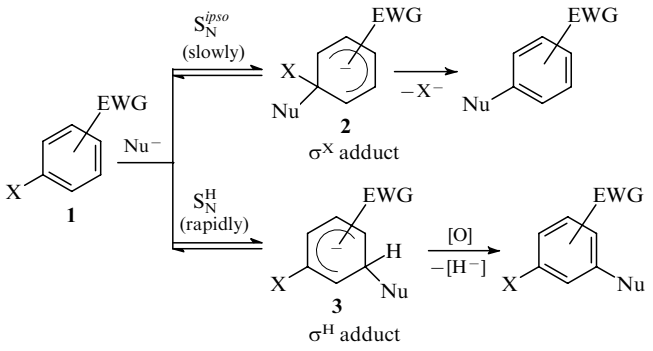
II. Main transformation paths of σ^H adducts

According to the modern notion of nucleophilic aromatic substitution reactions proceeding as 'addition – elimination', the first step of the nucleophilic attack on activated aromatic substrate **1** gives rise to intermediates of two types, *viz.*, σ^X adducts (Meisenheimer complexes) **2** or σ^H adducts (Servis complexes) **3**. Even in the presence of a leaving group in the ring, the *ipso*-substitution is

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always preceded by the rapid and reversible formation of σ^H adducts as kinetically controlled products.[4]



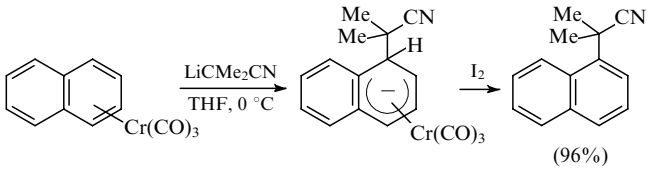
X is a leaving group; EWG is N_2, NO_2, NO, CO_2R, *etc*.

The σ^H adducts **3** differ substantially in stability. Thus, both unstable short-lived species and stable anionic complexes and dihydro compounds are known.[1] In the nitroarene series, the stability of σ^H adducts increases as the number of electron-withdrawing groups in the nucleus is increased. Thus, the existence of σ^H adducts, *viz*., di- and trinitrobenzene derivatives, was unambiguously proved, whereas the corresponding mononitrobenzene derivatives were not, to our knowledge, detected.

The σ^H intermediates derived from azines can be stabilised both by the introduction of electron-withdrawing groups, including the aza group, and through protonation of anionic forms and their transformations into neutral dihydro compounds. Clearly, the σ^H adducts generated from cationic forms of azines do not bear a charge. On the whole, σ^H adducts (Servis complexes) are generally more stable than their σ^X analogues (Meisenheimer complexes). The nature of the leaving group is the main factor responsible for the high stability of σ^H adducts. Unlike good leaving groups, such as Hal, CN, NO_2, SO_3H, *etc*., which are readily solvated as X^- anions, the hydride ion is not susceptible to solvation and it was not detected as a kinetically independent species in solutions. The occurrence of hydrogen in the form of the proton H^+ or the radical $H^\bullet$ is thermodynamically much more favourable than its occurrence as the hydride ion H^-. Therefore, aromatisation, which proceeds either through oxidative processes or with the involvement of auxiliary leaving groups (autoaromatisation) rather than *via* the direct abstraction of a hydride ion, is the bottleneck of S_N^H processes. Hence, nucleophilic attack on the unsubstituted carbon atom of arenes (hetarenes) affords (under particular conditions) S_N^H-reaction products. If none of the mechanisms of aromatisation takes place, σ^H adducts can undergo dissociation. This is particularly true for σ^H adducts generated from nitroarenes. The σ^H adducts derived from heteroarenes can be involved in alternative reactions resulting in the ring opening or recyclisation (for example, ANRORC transformations).[5,6]

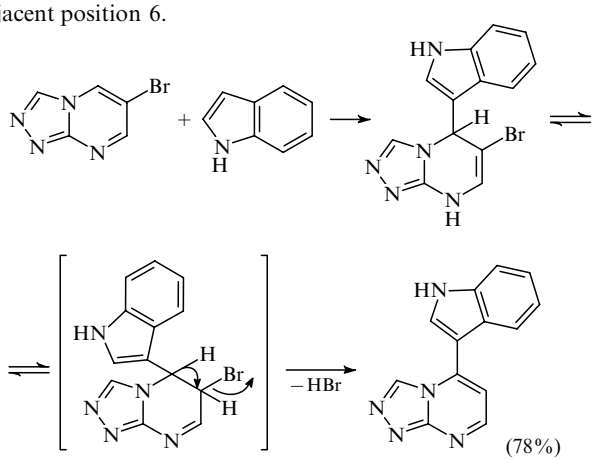
Oxidative aromatisation is a variation of the S_N^H reactions in which elimination occurs as a redox process.[1] In this type of reaction, both inorganic (atmospheric oxygen, halogens, hypohalogenites, sulfur, metal cations, *etc*.) and organic (quinones, triarylmethyl, tropylium and heterocyclic cations, *etc*.) reagents can be used as oxidisers. Besides, oxidative aromatisation can be performed electrochemically. In the absence of an oxidising agent, the starting π-electron-deficient arene (heteroarene) can serve as such a reagent. An oxidiser abstracts electrons from the σ^H adduct and hydrogen is most often eliminated as a proton.[1]

As an example of the oxidative S_N^H processes, we refer to the reactions of naphthalene activated by chromium carbonyl with organolithium compounds. The resulting σ^H adduct undergoes aromatisation under the action of elemental iodine.[7]

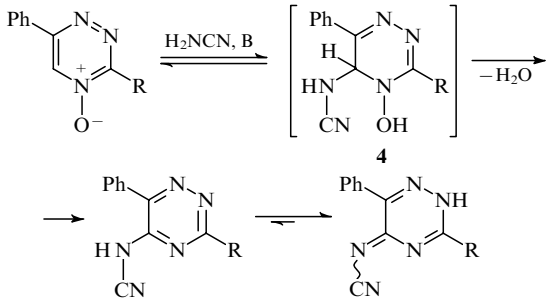


Autoaromatisation proceeds if the σ^H adduct contains a nucleofuge, which is initially present in either the substrate or the reagent. In this case, the nucleofuge group X (which is readily solvated) serves as an oxidiser and is eliminated together with the electron pair from the σ^H adduct as the X^- anion, whereas hydrogen leaves as a proton.

There are several types of autoaromatisation of σ^H adducts. If the leaving group is located in the aromatic ring in the *ortho* position with respect to the carbon atom subjected to the attack, these reactions are said to be *cine*-substitution reactions. Thus in the reactions of 6-bromoazolopyrimidines with indole and its derivatives,[8] the hydrogen atom at position 7 of the triazolopyrimidine system is replaced and the bromine atom leaves the adjacent position 6.



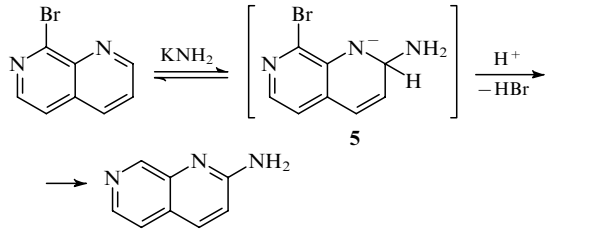
Numerous S_N^H reactions in the series of azine *N*-oxides and their derivatives (deoxygenative substitution of hydrogen)[9] belong to the *cine*-substitution processes. In this case, the *N*-oxide, *N*-alkoxide or *N*-acyloxy functional group serves as the auxiliary leaving group in the second step involving elimination of the hydrogen atom from the σ^H adduct. For example, in the reactions of substituted 1,2,4-triazine *N*-oxides with cyanamide, σ^H adduct **4** undergoes aromatisation through 1,2-elimination of the water molecule.[10]



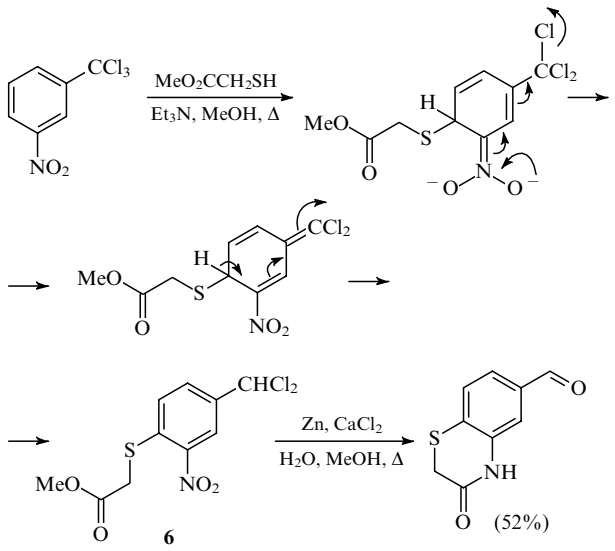
R = H, Et, Ph; B is a base.

If the reaction centre and the nucleofuge group X are separated by one or more atoms, the reactions are said to belong to *tele*-substitution processes. Here, the substituent X can be either bound to the aromatic nucleus (Scheme 1) or located in the side chain (Scheme 2). In the former case (see Scheme 1), the reactions proceed through the formation of σ^H adduct **5**, which undergoes aromatisation *via* 1,4-elimination of HBr with abstraction of the *tele*-arranged bromine atom.

Scheme 1

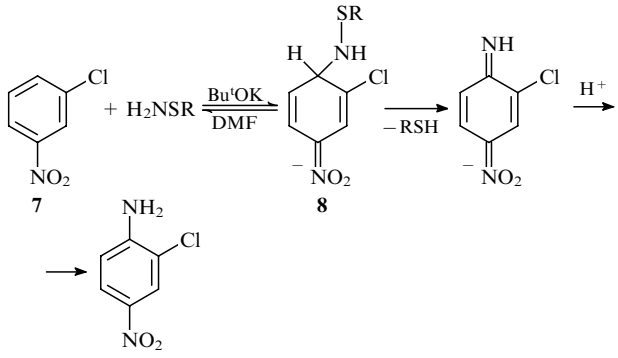


Scheme 2



In the latter case (see Scheme 2), aromatisation of the σ^H adduct is achieved through the abstraction of the chlorine atom from the trichloromethyl substituent. Reduction of S_N^H-reaction product **6** with zinc led to the thiazine-ring closure.[11]

The so-called vicarious nucleophilic substitution where a good leaving group X is present in the nucleophile residue belongs to well-studied autoaromatisation reactions of σ^H adducts.[12–15] For example, the attack of sulfenamides on the unsubstituted carbon atom of 3-chloro-1-nitrobenzene (**7**) afforded adduct **8** whose structure allows the RSH group to undergo β-elimination.[15]



Vicarious autoaromatisation of σ^H adducts readily proceeds in the case of azoles,[16] azines [17] and nitroarenes [17] and this process provides the basis for the construction of heteroaromatic systems, for example, of the indole [18,19] and quinoline [20] rings.

III. Construction of azine-based heterocyclic systems

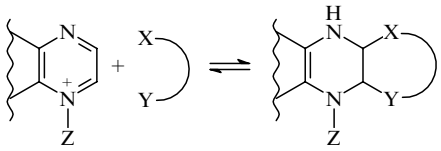
Azines containing two or more heteroatoms differ substantially from nitroarenes in that they can be subjected to the double nucleophilic attack. One-pot syntheses of fused heterocyclic systems are based on the tendency of azines to form cycloadducts in reactions with bifunctional nucleophilic reagents.

1. Tandem reactions $A_N - A_N$

There are a large number of examples of the construction of fused heterocyclic systems by the replacement of two adjacent good leaving groups in pyridine, quinoline, pyrimidine, pyrazine, quinoxaline and other rings under the action of bifunctional nucleophiles.[21] The main limitation of this method is that only azaaromatic compounds containing two nucleofuge groups at positions 1 and 2 can be used in such reactions.

The ability of unsubstituted azines to form cycloadducts in reactions with binucleophiles provides the basis for another procedure for the synthesis of fused heterocyclic systems.

It should be noted that although heterocyclic systems contain aza groups comparable to the nitro group in its electron-withdrawing properties, additional activation of the substrate is often required for the reaction to proceed. One of the commonly used procedures for the activation of azines in these transformations involves quaternisation of the nitrogen atoms in the ring. Some nucleophiles can react with azine salts. However, activation by acids is not necessarily applicable because it is accompanied by deactivation of the nucleophile. Another method involving alkylation of the azine ring is free from this drawback. The latter method was used in a large number of syntheses of fused heterocycles from *N*-alkylazinium salts. Thus, the *ortho*-cyclisation processes occurring in the reactions of 1,3-binucleophiles with quaternary 1,4-diazinium salts have been described.[20] One-pot syntheses of imidazopyrazines, imidazopteridines, furoquinoxalines, pyrroloquinoxalines, imidazoquinoxalines and thiazoloquinoxalines have been reported.[21] Table 1 gives examples of the construction of fused azine-based heterocyclic systems using tandem reactions of the $A_N - A_N$ type. All these systems were prepared by cyclisation of triazinium (**9**), *N*-alkylquinoxalinium (**10**), *N*-alkylpyrazinium or *N*-alkylpteridinium salts with such 1,3-binucleophiles as β-diketones, thioamides, dithiocarbamates, thiourea derivatives, *etc*.



X = H, Alk; X, Y are nucleophilic groups.

Unlike the $S_N^{ipso} - S_N^{ipso}$ reactions in which thiourea derivatives act as N,S-binucleophiles,[30–33] the $A_N - A_N$ reactions involve these derivatives exclusively as N,N′-binucleophiles.[34]

An important characteristic feature of the $A_N - A_N$ reactions is the reversible formation of cyclic products. Due to the reversibility of the double addition and ambident character of the nucleophiles used, these reactions can yield regioisomeric cyclisation products. For example, tetrahydrothiazolo[4,5-*b*]quinoxaline **11** formed by the reaction of the *N*-alkylquinoxalinium salt **10** with thioamide **12** under kinetically controlled conditions in aprotic solvents can be subjected to different types of isomerisation. Upon heating in ethanol, compound **11**, containing the aryl group in the side chain (R^2 = Ph), underwent isomerisation to give thiazoloquinoxaline **13**. When R^2 = Me, isomerisation proceeded with the involvement of the methyl group to give pyrrolo[2,3-*b*]quinoxaline-2-thione **14** as the cyclisation product.[21]

Due to the tendency of cycloadducts to dissociation, not only regio- but also stereoisomers can be generated. An example is the construction of the tetrahydropyrrolo[2,3-*b*]quinoxaline ring. The reaction under the kinetically controlled conditions (activation of the nucleophile with a base) gave rise to stereoisomer **15** having the *exo* configuration, whereas the reaction in the absence of a base afforded both the *exo* isomer and the thermodynamically more stable *endo* isomer **16**, the rearrangement **15** → **16** being possible.[35]

Table 1. Syntheses of fused heterocycles on the basis of 1,4-diazinium and triazinium salts with the use of A_N-A_N reactions.

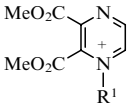
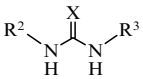
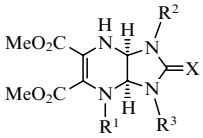
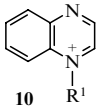
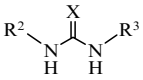
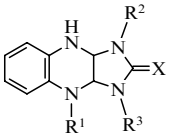
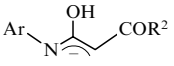
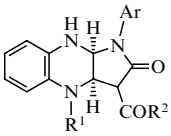
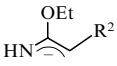
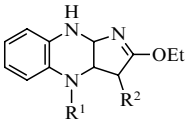
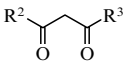
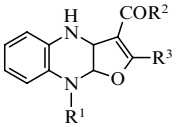
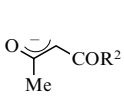
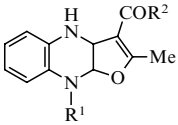
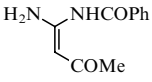
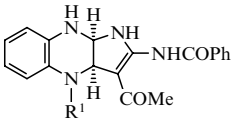
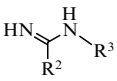
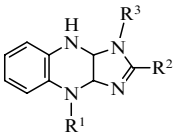
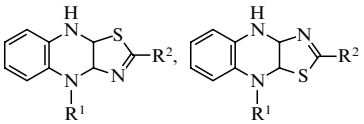
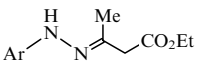
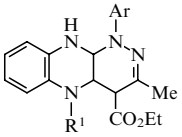
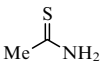
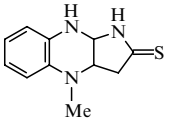
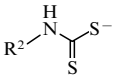
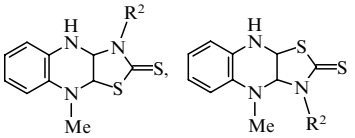
Substrate	Binucleophilic reagent	Product	Ref.
 R^1 = Me, Et.	 R^2, R^3 = H, Me, Ph, NH_2, NHPh; X = O, S.		21
 **10** R^1 = Me, Et.	 R^2, R^3 = H, Me, Ph, NH_2, NHPh; X = O, S.		21
	 R^2 = Me, Ph, 4-$MeOC_6H_4$, 2-Tol, 4-Tol, 4-ClC_6H_4.		21
	 R^2 = Ph, 4-$O_2NC_6H_4$.		21
	 R^2, R^3 = Me, OEt.		21
	 R^2 = Me, OEt, Bu^i.		21
			21
	 R^2 = Ph, 2-ClC_6H_4; R^3 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 2-Py.		21
	 R^2 = Me, Ph.		21
	 Ar = 4-$O_2NC_6H_4$, 2,4-$(O_2N)_2C_6H_3$.		21
10 (R^1 = Me)			21
	 R^2 = Bn, cyclo-C_6H_{11}, thiazol-2-yl.		21

Table 1 (continued).

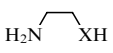
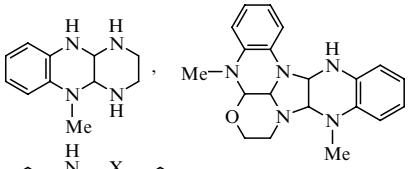
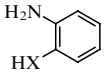
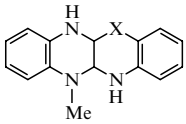
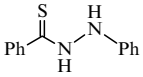
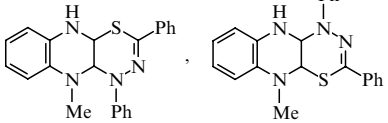
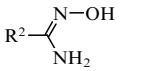
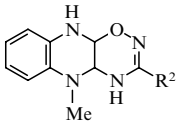
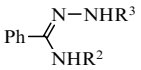
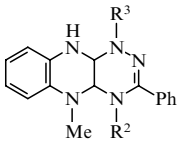
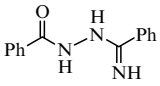
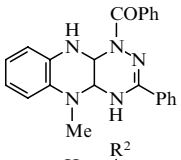
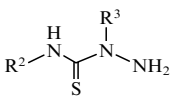
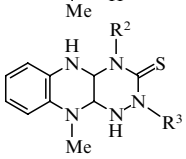
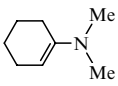
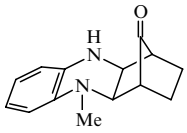
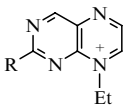
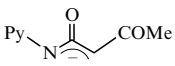
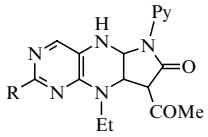
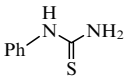
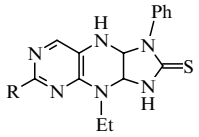
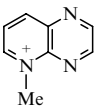
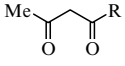
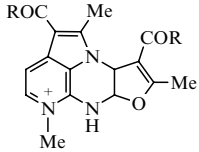
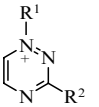
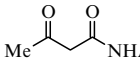
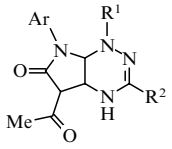
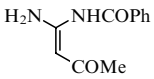
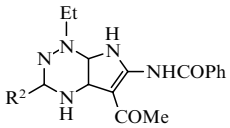
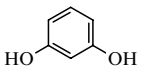
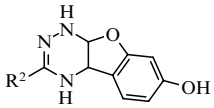
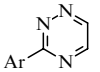
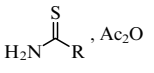
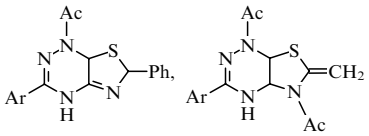
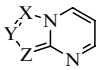
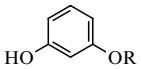
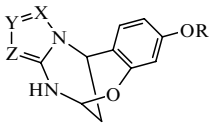
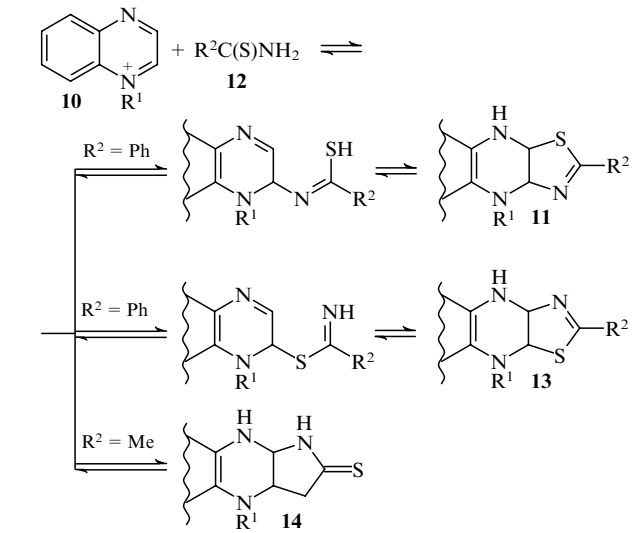
Substrate	Binucleophilic reagent	Product	Ref.
10 (R^1 = Me)	 X = NH, O.		21
	 X = NH, O.		21
			21
	 R^2 = Me, Ph, Bn, 4-BrC_6H_4.		21
	 R^2 = H, Ph; R^3 = H, COPh.		22
			21
	 R^2 = H, Ph; R^3 = Me, Ph.		21
			21
 R is morpholinyl.			23
			21
	 R^1 = H, Et; R^2 = SMe, morpholinyl.		21
 **9**	 Ar = Ph, 4-Tol, 2-HOC_6H_4.		24, 25

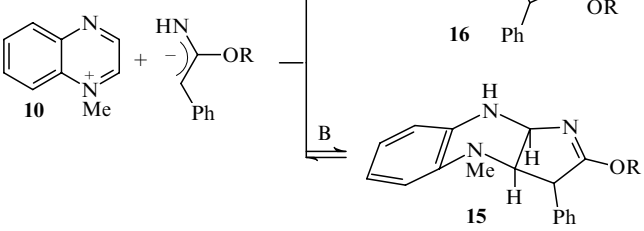
Table 1 (continued).

Substrate	Binucleophilic reagent	Product	Ref.
9 (R^1 = Et; R^2 = SMe, morpholinyl)			25
9 (R^1 = H; R^2 = SMe, NH_2)			26, 27
 Ar = Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$.	 R = Ph, Me.		28
 X = N, CCN; Y = N, CH, CCN, CSMe, CCF_3; Z = N, CCO_2Et.	 R = H, Me.		29

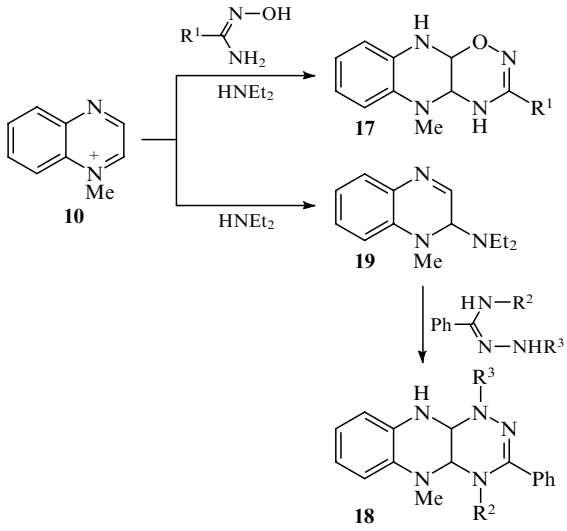
Note. In all reactions, the yields of the products were higher than 80%.



R^1 = Me, Et.



The reactions of 1,4-diazinium salts with 1,4-bifunctional nucleophiles are very similar to the annelation of five-membered rings to the pyrazinium ring. The reactions of *N*-alkyl-1,4-diazinium salts with 1,4-binucleophiles afforded a series of tetrahydropyrazines and tetrahydroquinoxalines fused with different heterocycles, such as pyrazine, oxazine, thiadiazine and triazine rings (see Table 1). For example, cyclisation of quinoxalinium salts with amide oximes and amidrazones afforded partially hydrogenated derivatives of new heterocyclic systems, *viz*., 1,2,4-oxadiazino- (**17**) and 1,2,4-triazolo[5,6-*b*]quinoxalines (**18**).[22]



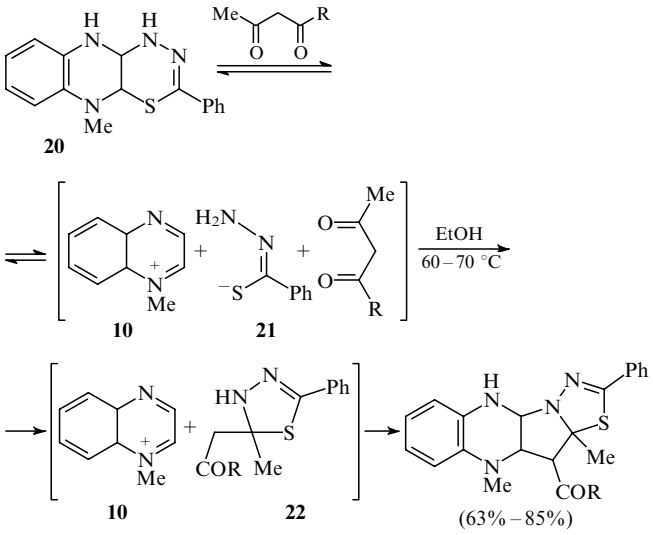
R^1 = Me, Ph, Bn, 4-BrC_6H_4; R^2 = H, Ph; R^3 = H, COPh.

The reactions with amidrazones were carried out with pre-isolated adduct **19** prepared by the reaction of the *N*-methylquinoxalinium cation **10** with diethylamine to prevent the formation of tetrazines from amidrazones in a basic medium.[22]

Like the products obtained in the A_N-A_N reactions of 1,4-diazinium salts with 1,3-binucleophiles, cycloadducts prepared by the addition of 1,4-binucleophiles to 1,4-diazinium salts readily undergo dissociative destruction and isomerisation in protic solvents in the presence of catalytic amounts of acids.[36]

Dissociation of the cycloadducts is initiated both by mineral acids[37] and CH-acids, in particular, by acetylacetone and acetoacetic esters. In the latter case, the reactions afforded new fused heterocyclic systems.[38] First, the starting thiadiazinoquinoxaline

20 dissociated to yield the quinoxalinium cation **10** and thiobenzhydrazide (**21**). The latter reacted with a β-dicarbonyl compound to give hydrazone, which underwent intramolecular cyclisation to form thiadiazole **22**. The final step involved the tandem reaction A_N-A_N in which the compound **22** acted as a binucleophile.

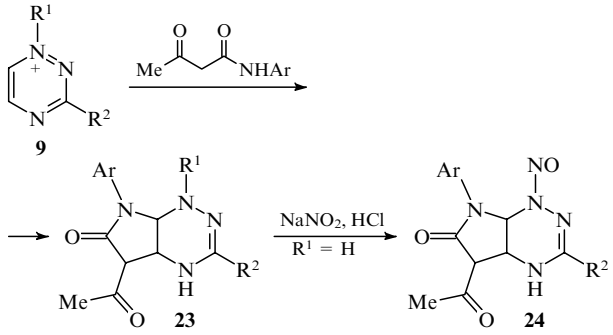


R = OAlk.

To prevent dissociation of the cycloadducts, the NH group of the tetrahydropyrazinium ring can be subjected to acylation.[21] The acyl derivatives are much more stable than the starting cycloadducts and do not dissociate even in acidic solutions.

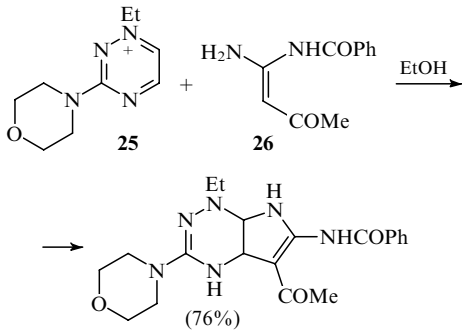
Another way of stabilising hydrogenated σ^H adducts is based on abstraction of hydrogen atoms together with the electron pair from the reaction centres in the presence of oxidising agents [1, 12] (oxidative S_N^H process). In some reactions, σ^H adducts are produced in quasistationary concentrations. Here the presence of an oxidising agent in the reaction mixture is a necessary condition for an arene to interact with a nucleophile. This type of reaction will be considered below.

1,2,4-Triazines are similar to 1,4-diazines in reactivity. In the reactions with binucleophilic reagents, these compounds are prone to form addition products at the *ortho*-atoms. For instance, protonated 1,2,4-triazines and their alkyl derivatives **9** readily reacted with acetoacetamides to give tetrahydropyrrolo[1,2,4]triazines.[24, 25] Cycloadducts **23** derived from protonated 1,2,4-triazines are unstable and can be isolated only as salts of trifluoroacetic acid. Dissociation of these compounds can be prevented by nitrosation of the nitrogen atom adjacent to the reaction centre. *N*-Nitroso derivatives **24** are more stable and could be isolated as free bases.[24]

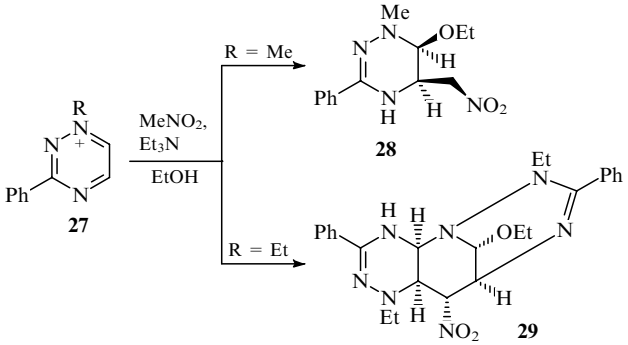


R^1 = H, Et; R^2 = SMe, morpholinyl.

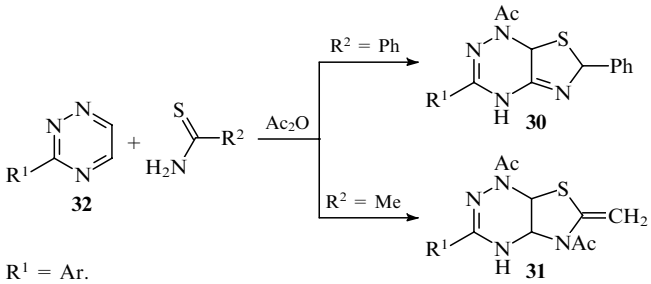
Another procedure for the synthesis of pyrrolotriazines involves the reaction of 1,2,4-triazine derivative **25** with ketene aminal **26**. These reagents, which are widely used in the inverse-electron demand Diels–Alder reactions,[39] react with triazinium salts as C,N-binucleophiles.[40]



The reactions of 1-alkyl-3-phenyl-1,2,4-triazinium salts **27** with nitromethane in the presence of triethylamine are extraordinary processes. Depending on the nature of the *N*-alkyl group, either one or two molecules of the triazinium salt can participate in these reactions giving rise to adduct **28** or cage compound **29**, respectively.[41] The reactions are accompanied by the addition of the solvent molecule (EtOH). In the latter reaction, nitromethane acts as a 1,1-binucleophile. This is a rare example of one-step syntheses of complex cage heterocycles.

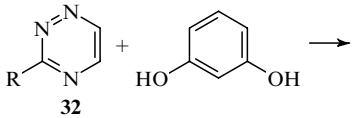


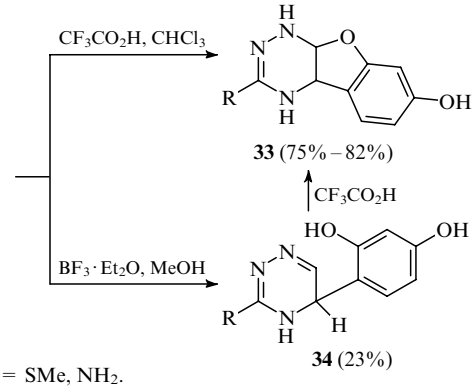
In addition to *N*-alkyltriazinium salts, *N*-acyl derivatives can also react with binucleophiles, activation by acylation often being advantageous over activation by alkylation.[28] Thus, a new approach to the synthesis of thiazolo[4,5-*e*][1,2,4]triazines **30** and **31** was proposed on the basis of the tandem nucleophilic addition of alkyl- and arylthioamides to 1,2,4-triazine derivatives **32** in acetic anhydride.[28] Attempts to prepare thiazolo[4,5-*e*][1,2,4]triazines from 1-alkyl-1,2,4-triazinium salts failed.



R^1 = Ar.

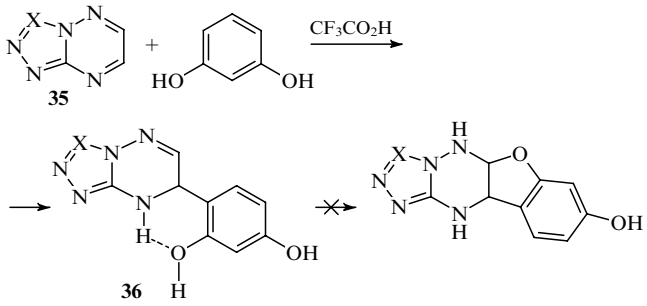
Aromatic ambident C-nucleophiles can participate in the A_N-A_N reactions with 1,2,4-triazinium salts.[26] For instance, 3-methylthio- and 3-amino-1,2,4-triazines **32** reacted with resorcinol in the presence of trifluoroacetic acid. The addition of the aromatic ring of resorcinol at the C(5) atom of the triazine followed by nucleophilic attack of the oxygen atom on the C(6) atom afforded benzofurotriazines **33**. Intermediate monoaddition product **34** was isolated only with the use of a softer activating agent, *viz*., boron trifluoride etherate.[26]





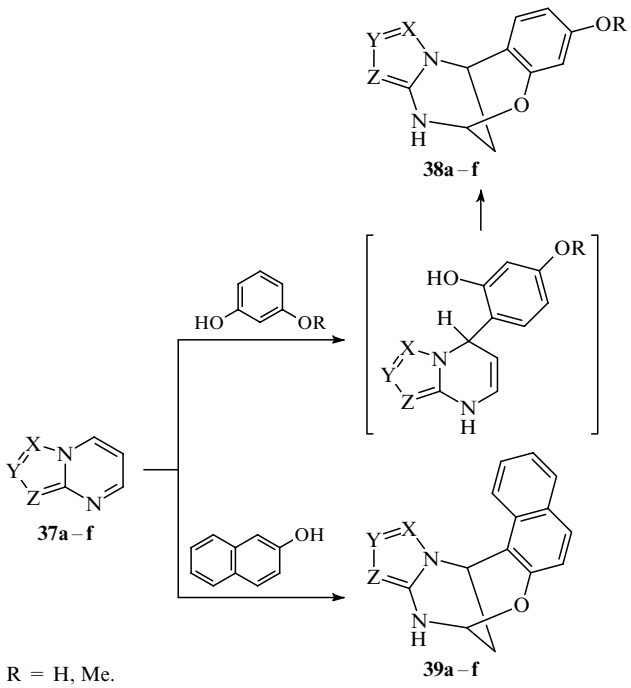
R = SMe, NH_2.

In the reactions with binucleophilic resorcinol, azolo-annelated 1,2,4-triazines **35** are more inert and their reactions stop at the stage of formation of monoaddition products.



X = CH, N.

This is attributable to the fact that the adduct **36** occurs predominantly in the conformation unfavourable for cyclisation, the conformation being stabilised by an intramolecular hydrogen bond.[27]



R = H, Me.

Compounds **37**, **38**, **39**	X	Y	Z
a	N	CH	CCO_2Et
b	CCN	CCN	N
c	N	CH	N
d	N	CSMe	N
e	N	CCF_3	N
f	N	N	N

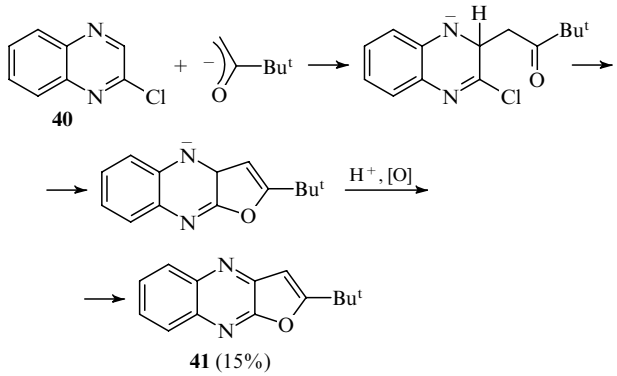
A different situation occurs when azines with the 1,3-arrangement of the heteroatoms are used as the substrate. These compounds tend to add binucleophiles at the atoms located in the *meta* positions of the heteroaromatic ring with respect to one another. Actually, the reactions of azolopyrimidines **37a–f** with 1,3-binucleophilic phenols gave rise to cage structures **38a–f** and **39a–f**.[29]

To summarise, it should be noted that the nature of the interactions of azinium cations with binucleophiles depends on the relative arrangement of the aza groups. The presence of heteroatoms at positions 1 and 4 (pyrazine, quinoxaline or 1,2,4-triazine rings) is most favourable for the formation of fused heterocycles. The reactions of diazines containing heteroatoms at positions 1 and 2 or at positions 1 and 3 are often accompanied by side reactions.[21] Examples of the construction of new heterocyclic systems *via* the addition of binucleophiles at the *ortho* or *meta* positions are few in number.[29,42]

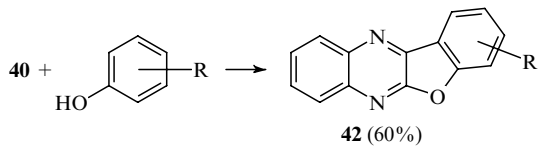
It should also be remembered that the A_N-A_N reactions are often complicated by the dissociation of primary cycloadducts formed under kinetically controlled conditions and their transformations into thermodynamically more stable compounds. These processes can be accompanied by changes not only in the regioorientation but also in the nature of the annelated ring. The $A_N-S_N^{ipso}$ and $S_N^H-S_N^{ipso}$ reactions considered in the following section lack this property.

2. Tandem reactions $A_N-S_N^{ipso}$ and $S_N^H-S_N^{ipso}$

Azaaromatic compounds containing heteroatoms at positions 1 and 4 can add binucleophiles to the unsubstituted carbon atoms at positions 2 and 3.[21] Let us consider the reactions of azines bearing a leaving group in one of these positions. The use of these substrates substantially increases the preparative potential of the reactions with binucleophiles due to a combination of the A_N, S_N^H and S_N^{ipso} processes. The transformations of this type can involve both non-activated azines and their quaternary salts. For example, the reactions of 2-chloroquinoxaline (**40**) with enolates led to the addition of the carbanion to the unsubstituted C(3) atom. The replacement of the chlorine atom in the resulting adduct followed by oxidation under the reaction conditions gave rise to furoquinoxaline **41**.[43]

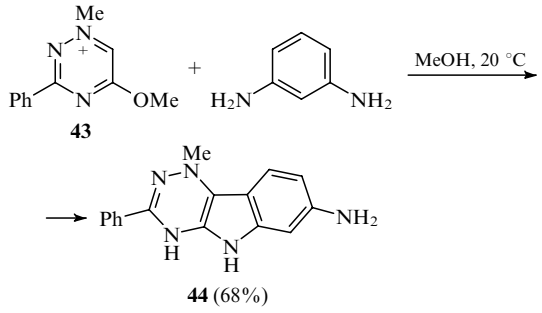


The reactions of 2-chloroquinoxaline with aromatic nucleophilic reagents proceed as the tandem sequence $S_N^H-S_N^{ipso}$ (apparently, with the involvement of hydrogen) to form benzofuroquinoxalines **42**.[44]

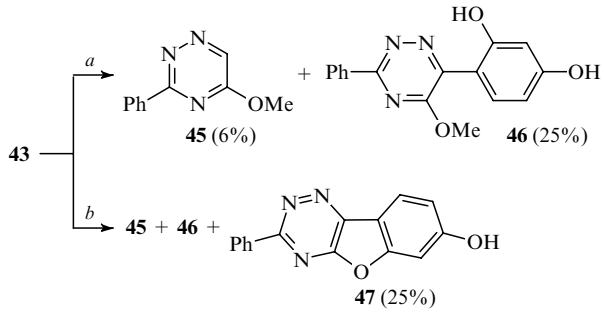


The presence of a leaving group possessing the electron-donating properties (for example, the methoxy group) in the azine ring leads to a decrease in the electrophilicity of the ring. The reactions with such non-activated substrates often do not take place. In this case, the azine ring can be activated with the use of a

conventional approach, *viz*., by quaternisation of the nitrogen atoms of the heterocycle. Thus, 5-methoxy-1-methyl-3-phenyl-1,2,4-triazinium tetrafluoroborate (**43**) is more reactive than its non-quaternised analogue and its reaction with *m*-phenylenediamine at 20 °C proceeded by the tandem process $A_N-S_N^{ipso}$ to form triazacarbazole **44**.[45]

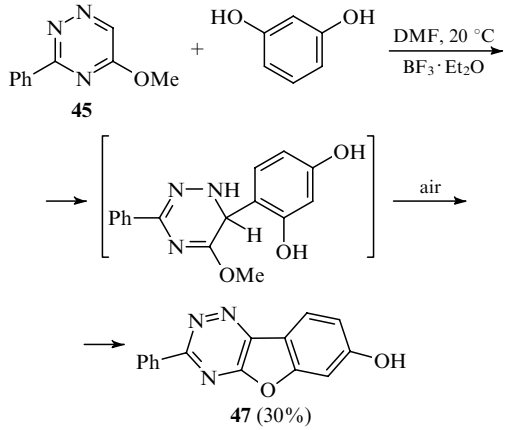


The reaction of the triazinium salt **43** with resorcinol proceeded through a cascade of transformations. This reaction was complicated by dequaternisation of the triazine ring to yield 5-methoxy-3-phenyl-1,2,4-triazine (**45**). The reaction afforded 6-(2,4-dihydroxyphenyl)-5-methoxy-3-phenyl-1,2,4-triazine (**46**) as the major product generated *via* the nucleophilic substitution of hydrogen in the triazine ring.[45]

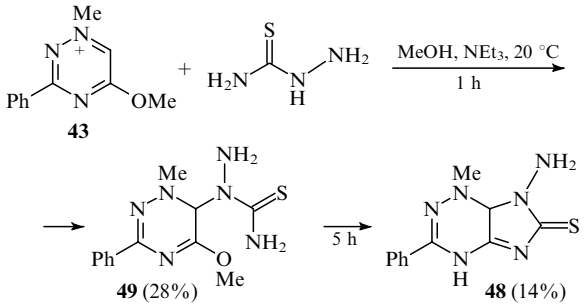


(*a*) resorcinol, methanol, Δ; (*b*) resorcinol, DMF, 20 °C.

The reaction performed in dimethylformamide afforded benzofurotriazine **47** as the major product generated through several reactions, *viz*., dequaternisation, S_N^H and S_N^{ipso}. It is most likely that the reaction involves dequaternisation as the first step followed by the attack of the nucleophile on the C(6) atom. In the final step, the methoxy group at position 5 is replaced and cyclisation occurs. This assumption was confirmed by a special experiment in which non-quaternised 5-methoxy-3-phenyl-1,2,4-triazine was used as the substrate (**45**). The latter reacted with resorcinol in the presence of boron trifluoride etherate to give benzofurotriazine **47**.

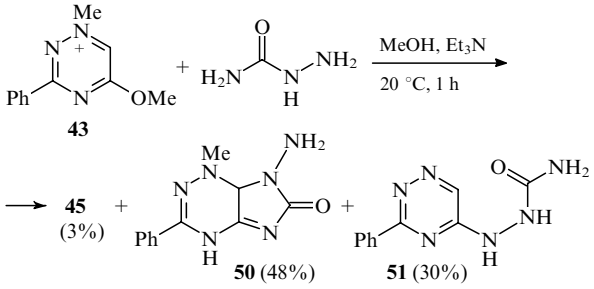


Analogously, triazinium salts react with *N*,*N*-binucleophiles.[45] The reaction of the salt **43** with thiosemicarbazide proceeded through the A_N and S_N^{ipso} transformations to yield imidazo[4,5-*e*][1,2,4]triazine-6-thione (**48**).



The isolation of intermediate **49** has been reported.[45] This is additional evidence that the unsubstituted carbon atom of the triazine ring is subjected to the initial nucleophilic attack, whereas the substitution of the nucleofuge (OMe) is a secondary process resulting in cyclisation.

It should be noted that the reaction can also follow the 'traditional' (S_N^{ipso}) pathway. The reaction of the salt **43** with semicarbazide afforded imidazotriazine **50** along with triazine **51**, which is a product of *ipso*-substitution of the methoxy group in 5-methoxy-3-phenyl-1,2,4-triazine **45** generated through dequaternisation of the substrate.[45]



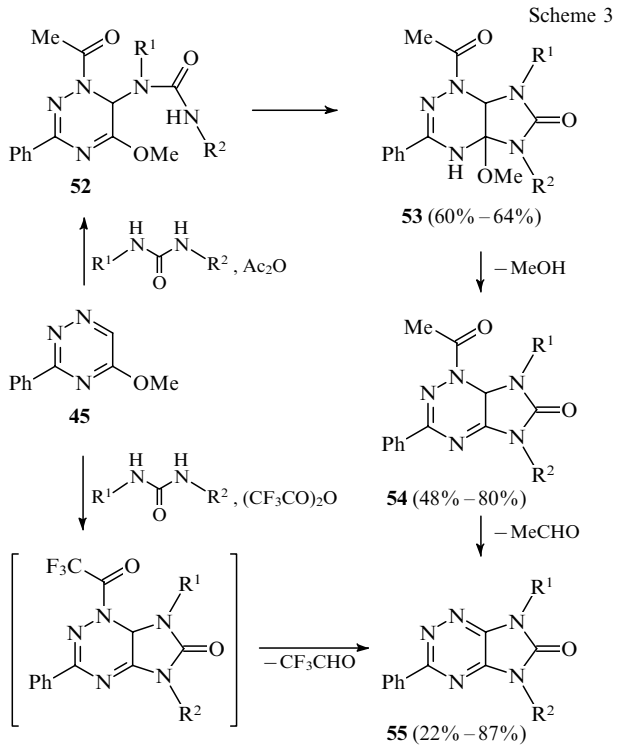
It is noteworthy that the nucleophilic attack in all the reactions under consideration occurs primarily on the unsubstituted carbon atom, although the methoxy group would be expected to be replaced according to the classical theory of nucleophilic aromatic substitution. Moreover, the methoxy group is located at position 5 of the 1,2,4-triazine ring, which is most reactive[46] with respect to nucleophiles. However, steric effects play the key role in these reactions[1] and σ^H adducts are initially generated in all processes. In the salt **43**, the methyl group at the N(1) atom adjacent to the reaction centre is responsible for substantial stabilisation of the compound **49**, which was isolated in the crystalline state. The reactions of the triazine **45** with nucleophiles (in particular, with semicarbazide) also can afford σ^H adducts upon attack on the C(6) atom. However, this process is reversible due to the absence of the methyl group at the nitrogen atom adjacent to the reaction centre and *ipso*-substitution of the methoxy group giving rise to compound **51** prevails.

The preparation of 6-azapurine derivatives by the reactions of 5-methoxy-1,2,4-triazines, for instance, of the compound **45**, with urea derivatives (Scheme 3) provides another example of the use of the $A_N-S_N^{ipso}$ and $S_N^H-S_N^{ipso}$ tandem reactions in the synthesis of fused heterocycles. In these reactions, acetic and trifluoroacetic anhydrides were used for activation of the substrate.[46]

The reactions of *N*-acyl-1,2,4-triazinium salts generated *in situ* with urea derivatives include a series of successive steps. Depending on the nature of the reagents and reaction conditions, both open-chain adducts **52** and their cyclisation products **53**–**55** can be isolated (see Scheme 3).[47]

The use of acylating reagents makes it possible, first, to activate the triazine ring to nucleophilic attack and, second, to stabilise a σ^H adduct. Besides, the acyl substituent can serve as an auxiliary group responsible for the occurrence of the S_N^H reaction. For example, the final step of the reaction of the 1,2,4-triazine **45**

Scheme 3



R^1, R^2 = H, Me.

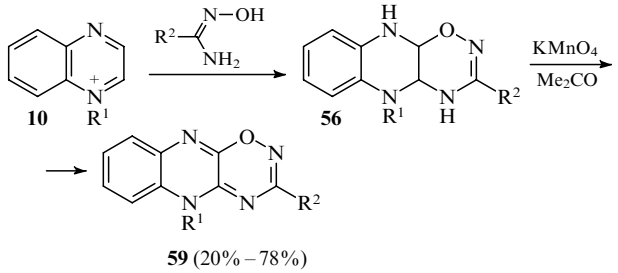
with urea derivatives involves elimination of acetic or trifluoroacetic aldehyde from the σ^H adduct, *i.e.*, the process as a whole can be considered as a variation of *cine*-substitution reactions.

Note also that the reaction of compound **45** with dimethylurea at 20 °C stopped at the stage of formation of adduct **53**, which is a cyclic Meisenheimer complex. The latter was isolated in the crystalline state. This is a rare example of a reaction proceeding according to the S_N^{ipso} scheme in which an intermediate was isolated.[2]

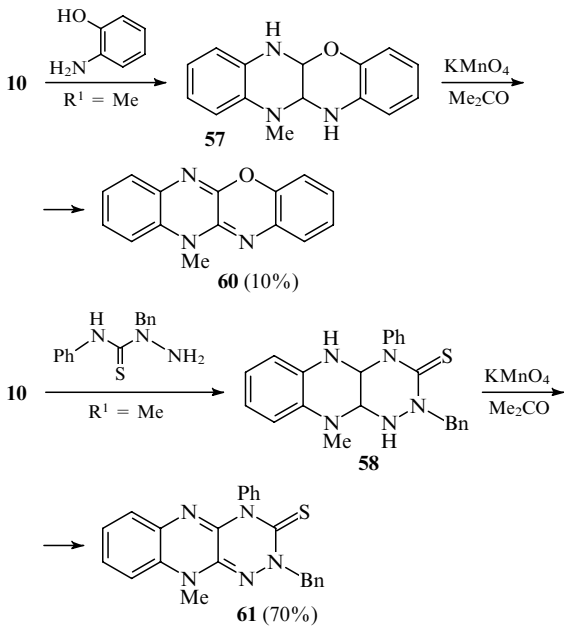
To summarise, combination of the A_N and S_N^H strategies with *ipso*-substitution is, undoubtedly, a powerful tool for the construction of various fused heterocyclic systems. The only limitation is that there is a need to synthesise a substrate containing a leaving group in the position required for cyclisation. However, this drawback is compensated by the high stability of the resulting products and the fact that they cannot undergo dissociation, which is often observed in the $A_N - A_N$ reactions.

3. Tandem reactions $S_N^H - S_N^H$

Only a few examples of the double nucleophilic substitution of hydrogen are known. All these reactions involve oxidative aromatisation of σ^H adducts.[48,49] Thus, oxidation of cycloadducts **56**–**58**, which were prepared by the $A_N - A_N$ reactions of quinoxalinium salts, by potassium permanganate led to their aromatisation.[48]

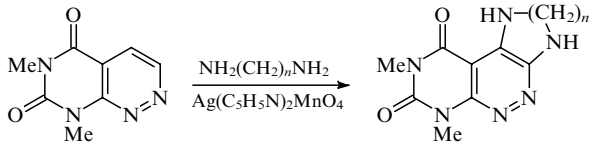


R^1 = Alk; R^2 = Me, Ph, Bn, 4-BrC_6H_4.



In this case, the S_N^H process is a convenient way of stabilising σ^H adducts. Compounds **59**–**61**, unlike their partially hydrogenated analogues, cannot undergo dissociation at all.

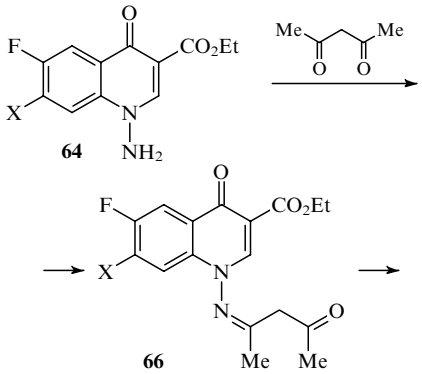
To our knowledge, the reactions of pyrimido[4,1-*c*]pyridazines **62** with diamines in the presence of an oxidising agent are the only examples of the tandem reactions $S_N^H - S_N^H$ proceeding *in situ* without isolation of intermediate σ^H adducts.[49] The reactions involve the addition of the nucleophile at position 4 of the heterocyclic system followed by intramolecular cyclisation to form tricyclic product **63**.

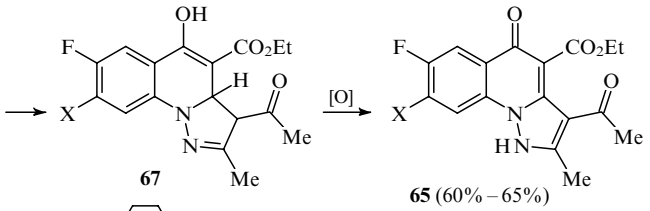


n = 2–4.

4. Intramolecular S_N^H reactions

New heterocycles are often generated by the intramolecular attack of a nucleophilic functional group present in the side chain of the heterocyclic substrate. The intramolecular S_N^H reactions were used for structural modifications of fluoroquinolone antibiotics.[50,51] For example, the reactions of 1-amino-substituted fluoroquinolones **64** with acetylacetone afforded tricyclic compound **65**.[50]

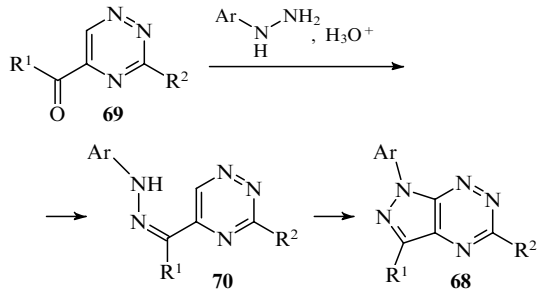




X = F, Cl, .

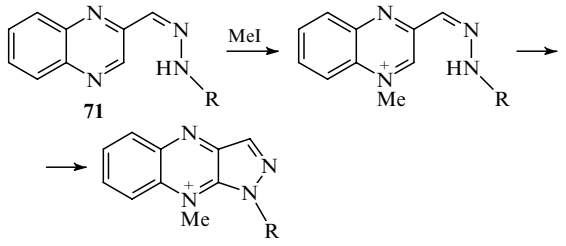
The mechanism of formation of the tricyclic product **65** involves condensation of the *N*-aminoquinolone **64** with acetylacetone followed by the intramolecular nucleophilic attack on the C(2) atom of the resulting diketone **66** and oxidation of σ^H adduct **67** with atmospheric oxygen.

The synthesis of pyrazolo[4,3-*e*][1,2,4]triazines **68** using the reactions of 5-acyl-1,2,4-triazines **69** with arylhydrazines in an acidic medium is another example of the intramolecular S_N^H process.[52]



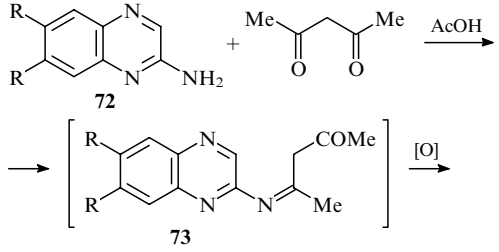
R^1 = Me, Et, Pr^n; R^2 = Ph, SMe; Ar = Ph, 4-Tol, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$.

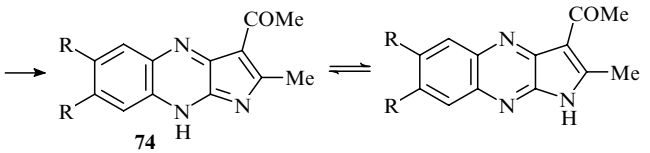
This synthesis involved the successive formation of hydrazones **70** and intramolecular substitution of hydrogen.[52] Analogous transformations were also observed upon alkylation of quinoxaline-3-carbaldehyde hydrazones **71**. These reactions led to the intramolecular nucleophilic substitution of hydrogen at the α position with respect to the quaternary nitrogen atom.[53]



R = H, Me, Ph, Bn, 4-$O_2NC_6H_4$, 4-$O_2CC_6H_4$.

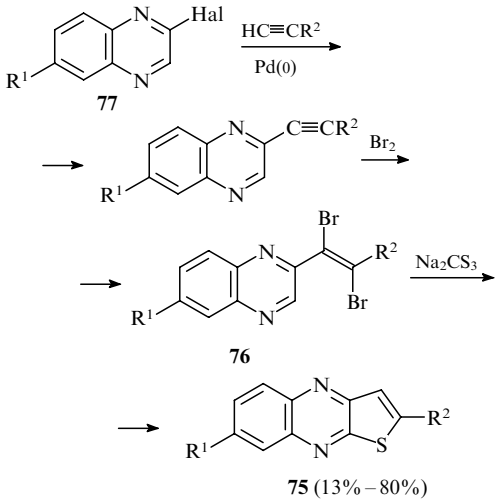
Yet another example of the intramolecular oxidative nucleophilic substitution of hydrogen is the reaction of 2-aminoquinoxaline **72** with acetylacetone or cyclohexanone.[54] Schiff's bases **73** generated in the course of the reactions underwent spontaneous cyclisation to pyrrolo[2,3-*b*]quinoxaline derivatives **74**.





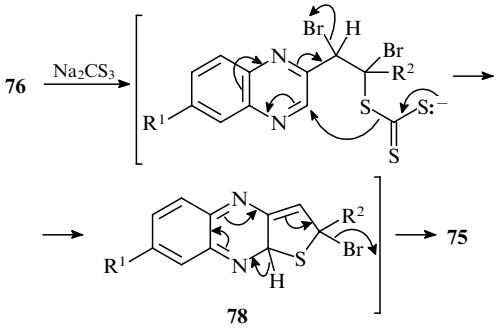
R = H, F.

The intramolecular *tele*-substitution to form thienoquinoxalines **75** was observed upon treatment of compounds **76** derived from chloro- or iodoquinoxaline derivatives **77** with sodium trithiocarbonate.[55]

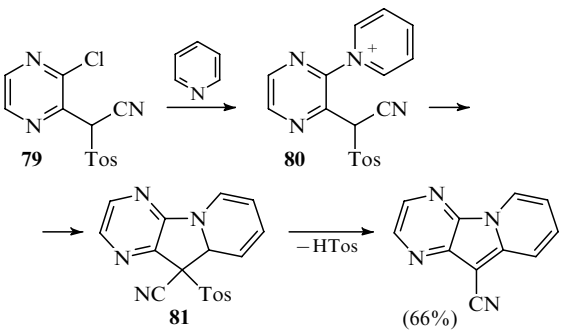


R^1 = H, Cl; R^2 = H, $SiMe_3$, Bu^n, Bu^t, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 4-ClC_6H_4, 4-IC_6H_4, 5-$F_3CC_5H_3N$.

Aromatisation of σ^H adduct **78** occurred through elimination of the bromine atom from the thiophene ring that formed.

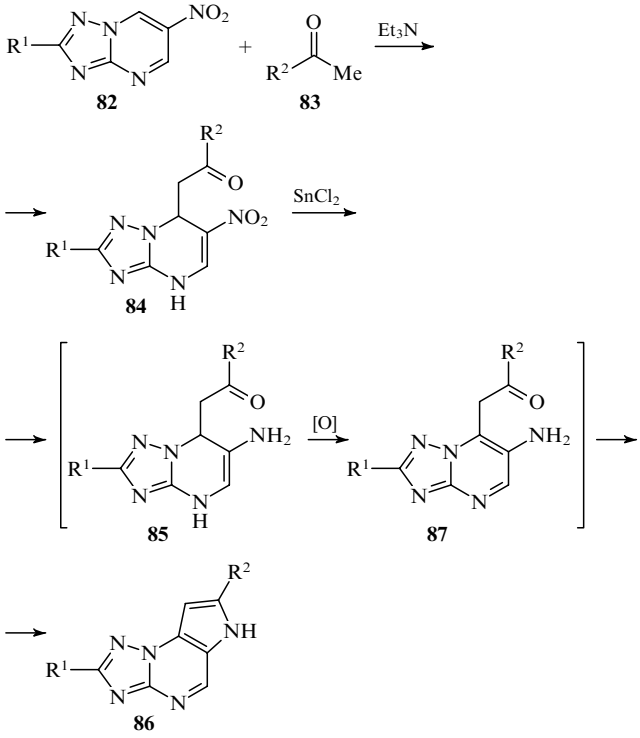


The reaction of pyrazine **79** with pyridine provides an interesting example of an intramolecular S_N^H reaction.[56]



This reaction was not completed by the formation of product **80** by the *ipso*-substitution of the chlorine atom. Under the action of an excess of pyridine, the carbanionic centre was generated in the side chain of the pyrazine ring and intramolecular cyclisation took place. Cycloadduct **81** underwent aromatisation through elimination of the proton together with the tosyl substituent.

For nitroarenes, commonly used procedures for the construction of heterocycles are based on the nucleophilic substitution of hydrogen followed by cyclisation of the S_N^H-reaction product involving the *ortho*-substituent.[14] This strategy, as applied to compounds of the heterocyclic series, is exemplified only by the reactions of 6-nitrotriazolo[1,5-*a*]pyrimidines **82** with acyl derivatives **83** of aromatic and heteroaromatic compounds giving rise to products of addition at the C(7) atom (**84**).[57]



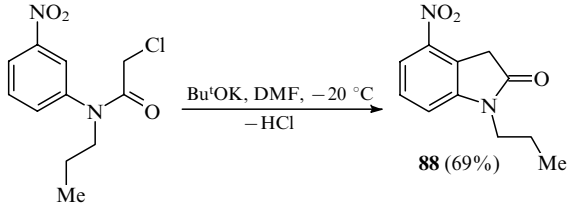
R^1 = H, Me; R^2 = Ph, 4-HalC_6H_4, 2-thienyl, 2-furyl.

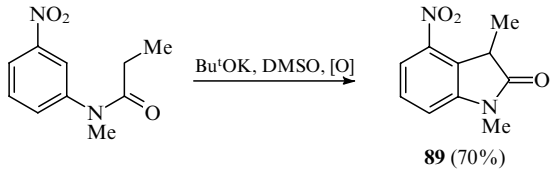
Reduction of the nitro group in the adducts **84** by tin(II) chloride did not stop at the formation of the corresponding amine **85** and afforded triazolopyrrolopyrimidine **86** as a result of oxidative aromatisation of the amine **85** followed by intramolecular cyclisation of product **87**.

IV. Construction of nitroarene-based heterocyclic systems

Most of the procedures for the direct annelation of heterocycles to nitroarenes consist in intramolecular S_N^H processes followed by cyclisation. In spite of the fact that the ring closure is not necessarily associated with the nucleophilic attack on the unsubstituted carbon atom, the S_N^H reactions of nitroarenes with binucleophiles are the key steps in these syntheses. These methods open up approaches to a wide range of biologically active indoles and quinolines, including those of natural origin. Since these methods have been surveyed in the recent review,[14] we consider these questions only briefly.

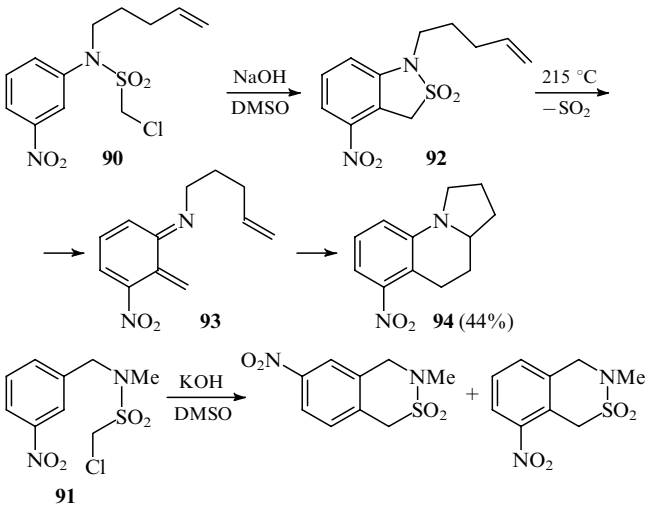
Procedures for annelation of five- and six-membered heterocycles to nitroarenes are based on oxidative and intramolecular vicarious nucleophilic substitution of hydrogen. The syntheses of nitroxyindoles **88**[58] and **89**[14] are examples. In the former case,





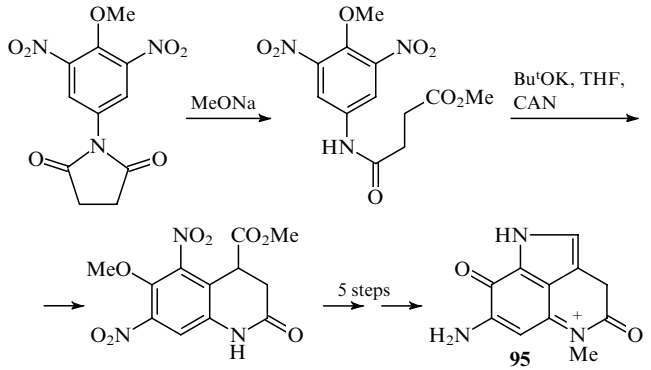
aromatisation of the σ^H adduct proceeds through the vicarious mechanism. The latter reaction involves oxidative aromatisation.

The intramolecular vicarious substitution of hydrogen in nitrophenyl- (**90**) and nitrobenzylchloromethylsulfonamides (**91**) led to annelation of five- and six-membered rings, respectively, to the arene ring.[59–62]



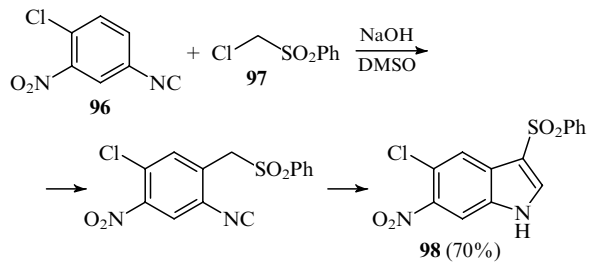
Interestingly, the initially formed cyclisation product **92** can be readily transformed into the quinoline derivative. Thermolysis of the compound **92** led to SO_2 extrusion with the formation of azaxylylene **93**. The subsequent intramolecular [4 + 2]-cycloaddition afforded tetrahydroquinoline **94**.[59–62]

The intramolecular S_N^H reactions can be employed for the preparation of the key compounds used in the syntheses of some natural substances. For instance, the synthesis of the natural antitumour drug makaluvamine C (**95**) found in marine sponges involved the closure of the six-membered ring on the basis of the oxidative S_N^H reaction.[63,64]

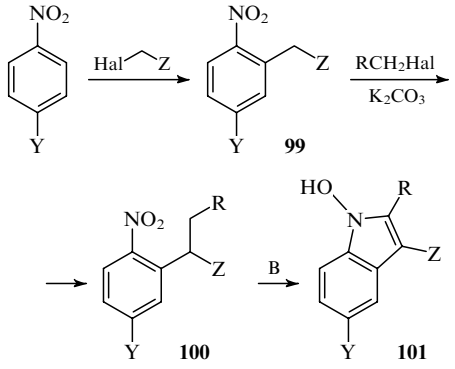


CAN = $(NH_4)_2Ce(NO_3)_6$.

The reactions of nitroarenes with bifunctional nucleophilic reagents can be accompanied by intramolecular cyclisation with the participation of such substituents in the aromatic substrate, as CN, NO_2, *etc*. For example, the presence of the amino group in substituted *m*-nitroanilines made it possible to synthesise indole derivatives by its reactions with acetophenones[65] or phenylacetonitrile.[66] Isocyanonitrobenzenes can also be involved in analogous transformations. Thus, the product of the S_N^H reaction of compound **96** with α-chloromethyl sulfone **97** underwent spontaneous cyclisation to give nitroindole **98**.[67]

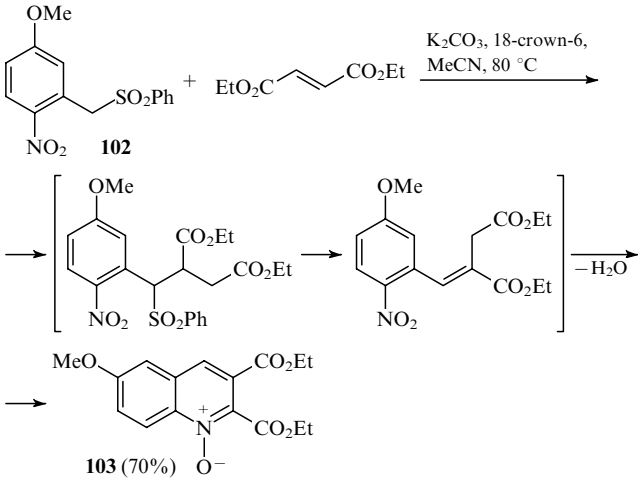


In some cases, cyclisation of nitroarenes proceeds with the involvement of the nitro group itself. For instance, nitrophenylacetonitriles **99** (Z = CN) generated by the S_N^H reactions can be readily alkylated. The resulting compounds **100** contain the nucleophilic centre in the side chain. In the presence of bases, these compounds undergo cyclisation involving the nitro group to yield *N*-hydroxyindole derivatives **101**.[19, 68, 69]

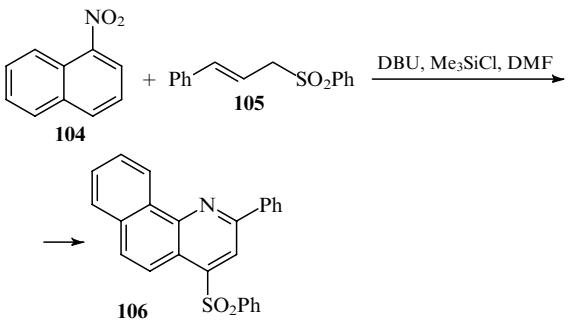


Y = Cl, Br, OMe; Z = CN, CO_2Bu, Tos, SO_2Ph;
R = Et, n-C_7H_{15}, CH=CH_2, CO_2Et, $CONMe_2$.

This approach can also be used in the annelation of a six-membered ring to an arene ring. For example, benzyl sulfone **102** was subjected to Michael condensation with α,β-unsaturated esters of carboxylic acids. In the presence of bases, the intermediate generated in this process underwent a series of transformations involving the nitro group to form quinoline *N*-oxide **103**.[14]

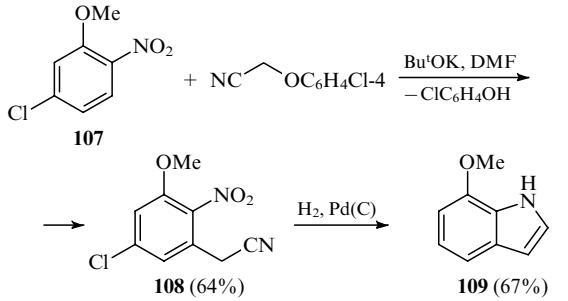


The reactions in which the heterocycle closure takes place *in situ* without isolation of intermediates are of particular interest.[20] For example, the reaction of nitronaphthalene **104** with sulfone **105** was not completed by the formation of the σ^H adduct. Under the reaction conditions, this adduct underwent aromatisation through an intramolecular redox process and cyclisation to give quinoline derivative **106**.

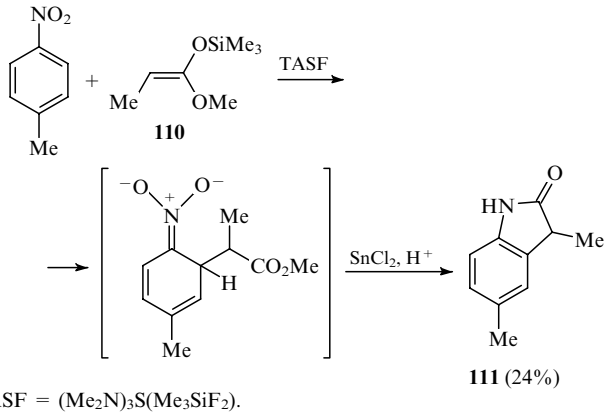


DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene.

The syntheses in which annelation of the heterocycle proceeds with the participation of the amino group generated by reduction of the nitro group of nitroarenes can be considered separately. In these syntheses, acetonitrile and acetophenone derivatives, silyl ethers of ketones, CH-active derivatives of carboxylic acids and other polyfunctional derivatives are used as nucleophiles. Both S_N^H-reaction products and σ^H adducts can be subjected to reductive cyclisation. For example, the reaction of *o*-nitroanisole **107** with (4-chlorophenoxy)acetonitrile was accompanied by vicarious nucleophilic substitution S_N^H to produce cyanomethyl derivative **108**. Reduction of the latter led to annelation of the pyrrole ring to the anisole ring to give methoxy-substituted indole **109**.[68]



Examples of reductive cyclisation of σ^H adducts of nitroarenes have been reported. Thus, the σ^H adduct formed in the course of the fluoride-induced addition of trimethylsilyloxyethylene **110** to nitroarenes underwent cyclisation into indolin-2-one **111** under the action of tin(II) chloride.[69]



TASF = $(Me_2N)_3S(Me_3SiF_2)$.

V. Conclusion

In the present review, we generalised and analysed the reactions of azines and nitroarenes containing at least one unsubstituted aromatic carbon atom with bifunctional nucleophilic reagents. These transformations were considered in the context of the construction of fused heterocycles. All the above-considered syntheses share a common trait, *viz*., the initial attack of a nucleophile on the unsubstituted carbon atom of azine or nitroarene to give σ^H adducts, which are generated rapidly and

reversibly regardless of the presence of nucleofugal groups in the substrate. Subsequent transformations of σ^H adducts depend on the nature of the substrate and nucleophilic reagent.

The formation of cyclisation products is most typical of azines containing heteroatoms at positions 1 and 2, 1 and 3 or 1 and 4. Cycloadducts prepared by the A_N-A_N reactions can be subjected to dissociation and isomerisation. These products can be stabilised by acylation, nitrosation, alkylation or further S_N^H-transformations. Fused heterocycles prepared in the tandem reactions $A_N-S_N^{ipso}$ and $S_N^H-S_N^{ipso}$ are more stable and are not prone to isomerisation.

To construct heterocycles from nitroarenes, it is most often necessary to introduce an additional functional group into the aromatic ring although the nitro group by itself can be of use.

To summarise, the data surveyed in this review provide evidence that nucleophilic attack on the unsubstituted carbon atom of azines and nitroarenes is a powerful tool for the synthesis of fused heterocycles.

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