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MOLECULAR COMPLEXES OF HETEROAROMATIC *N*-OXIDES AND THEIR REACTIONS WITH NUCLEOPHILES

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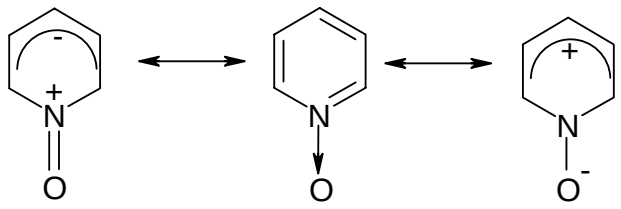
Abstract – It was shown that binding of heteroaromatic *N*-oxides in molecular complexes with appropriate v- and π-acceptors facilitates the nucleophilic substitution and addition reactions.

INTRODUCTION

It is well known that heteroaromatic *N*-oxides, unlike the corresponding nitrogen heterocycles, show much greater reactivity towards not only electrophilic but also nucleophilic reagents.[1,2] This reactivity is caused by the ambident character of the *N*-oxide group, that can serve as both an electron-withdrawing and an electron-acceptor:



The formation of molecular complexes with *N*-oxides is accompanied by redistribution of the electron density in donor and acceptor molecules. There may be three types of donor-acceptor interactions: formation of a stable complex; substantial intermolecular transformations within those complexes resulting in the formation of new compounds; subsequent secondary reactions of new complexes with other reagents.

Stable *N*-oxide adducts with various acceptors were discussed in our previous review.[3] Since unstable complexes are important for the study of reaction mechanisms and the development of new methods of organic synthesis when they act as intermediates or starting substrates, they will be discussed below. Usually, nucleophilic substitution of nitrogen-containing groups and halogen atoms conjugated with the

N-oxide group proceeds quite easily with strong nucleophiles (alkoxides, phenoxides, and alkylthiols). With weaker nucleophiles, however, substitution can be achieved only under more drastic conditions.

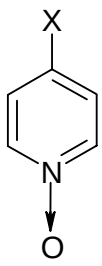
It is generally believed that any factor that is likely to decrease electron density in the heterocyclic ring facilitates its attack by nucleophiles. The following methods are usually used for this purpose: increasing the positive charge on the nitrogen atom in *N*-alkyl or *N*-acyl derivatives, introducing electron-withdrawing substituents into the ring or using of metal carbonyls.[4]

We proposed a new method of activation of *N*-oxide heterocycles towards nucleophiles: the formation of molecular complexes (MC) or charge transfer complexes (CTC) with v- or π-acceptors. Thus eg, in the previous paper[5] we showed several examples where binding of aromatic *N*-oxides in MC with tetracyanoethylene (TCNE), chloranil (CA) and bromanil (BA) can be applied to enhance their electrophilicity.

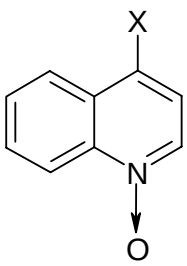
New applications of v- and π-acceptors in reactions of *N*-oxides with nucleophilic reagents and their mechanisms are discussed in this review. The review is mainly based on the results obtained by the authors.

1.1 COMPLEXES WITH π-ACCEPTORS

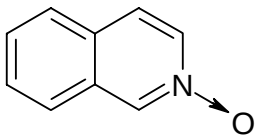
Special emphasis is made on the study of aromatic *N*-oxide (**1- 4**) complexes with π-acceptors (**5**) and **(6)**.[6]



1a-g



2 a-h



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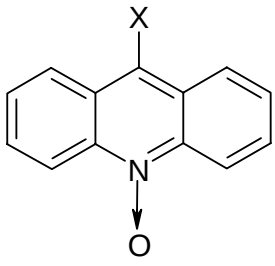
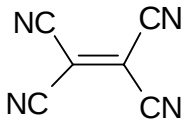
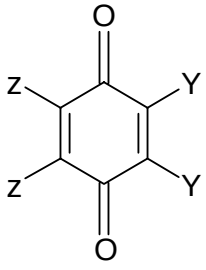


4 a-c

a) X= H, b) X= NO_2, c) X= Cl, d) X=CH_3, e) X= OCH_3, g) X= OC_2H_5, h) X= SCH_3



5



6 a-c

a) Z= Y= Br
b) Z= Y= Cl
c) Z=Cl, Y= CN

The complexes usually exist only in solutions in equilibrium with their components, and they cannot be isolated in the solid state. It is known that π-acceptors' activity is determined by their electron affinity (E_a). However, in practice, electrochemical reduction potentials that are proportional to E_a and can be easily determined by polarography, are used. These values for the compounds studied are listed in Table 1. It can be seen that **6a** is the least active acceptor, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, **6c)** is the most active one.

Table 1

Electrochemical reduction half-wave potentials of π-acceptors[7]

Acceptor	**6a**	**6b**	**5**	**6c**
E_a, V	0.00	+0.01	+0.15	+0.51

Due to the interaction between *N*-oxides and π-acceptors (**5**) and (**6a-c**) new absorption bands appear in solution in the visible region of the spectrum as a result of complex formation (Table 2).

Table 2

Absorption maxima of charge transfer complexes of *N*-oxides with π-acceptors in chloroform

N-oxide	*IP* (eV)	Acceptors; CTB λ_{max} (nm)			
		6a	**6b**	**5**	**6c**
1a	8.82		422	433	470
1c	8.76	395	416	440	478
1d	8.61	408	430	460	492
1e	8.40			492	532
1g	8.47		446	480	
2a	8.40	455		491	541
2b	8.83	-	-	432	
2c	8.41	453	457	490	531
2e	8.22	501	495	522	577
2h	8.04			555	
3	8.70	416		448	509
4a	7.77			615	716
4c	7.79			610	710

Frey obtained the empirical equation which correlates the position of the charge transfer band (CTB) maxima with the donors' ionization potentials (*IP*) for complexes of over 260 compounds with TCNE.[8]

$$\lambda_{max} = 1240/(0.81IP - 4.28)$$

Using this equation we calculated ionization potentials for the aromatic *N*-oxides (Table 2). As expected, the values of *IP* decrease from pyridine to acridine *N*-oxides, and when electron-donor substituents are introduced in the ring.

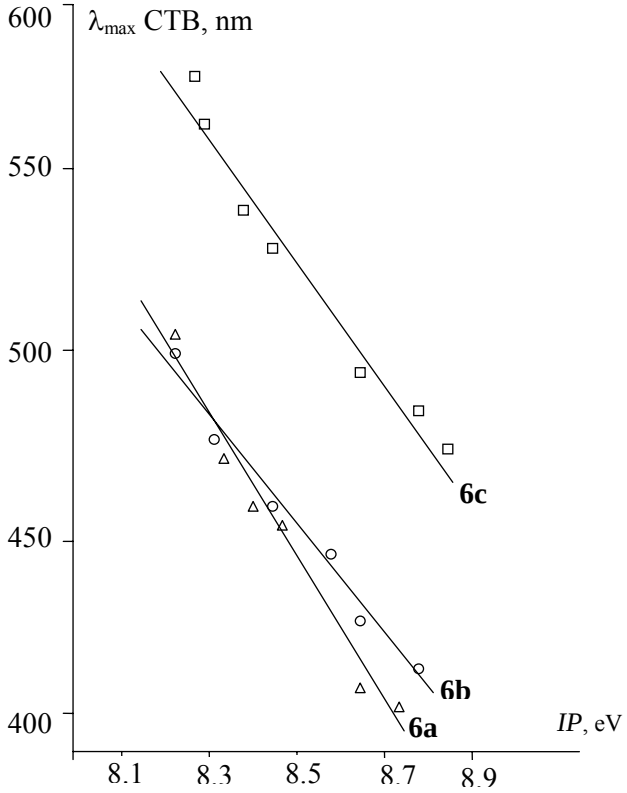


Figure 1. Dependence of CTB maxima of the complexes of *N*-oxides with various π-acceptors on ionization potentials of *N*-oxides - λ_{max} (for various acceptors).

Then the dependence of the calculated IP values on λ_{max} of CTB in complexes of N-oxides with other π-acceptors (**6a-c**) was determined (Figure 1). The linear correlations confirm the fact of CTC formation in these reactions. For more detailed research on the molecular complexes we resorted to the Benesi – Hildebrand method. Equilibrium constants of complex formation reactions were determined as well as their stoichiometric composition and extinction coefficients. The stoichiometric composition of all the complexes was found to be 1:1, and the equilibrium constants of complex formation increased with donor and acceptor strengths.

Equilibrium constants of complex formation give a linear correlation with σ^+- constants of substituents in the *N*-oxides (Figure 2).

As was already mentioned, most CTC of *N*-oxides with π-acceptors exist only in solutions. The only exceptions are quinoline and isoquinoline *N*-oxide complexes with compounds (**6a**) and (**6b**) and 4-chloroquinoline *N*-oxide with TCNE, which were isolated in the solid state. They are highly-fusible colored crystals. The stoichiometry of the complex with bromanile (*N*-oxide – **6a**) is 2:1, and with *N*-oxide - **6b** is 1:1. IR spectra of CTC with halogenaniles exhibit only slight shifts of the *N*-O bond vibrations. This fact indicates that the oxygen atom of the *N*-oxide group does not participate directly in

the complex formation, and it provides ground of the π,π-complex formation. The PMR spectra of these complexes contain only signals of aromatic protons which are shifted downfield by 0.05 – 0.1 ppm relative to signals of *N*-oxide protons. It should be mentioned that π,π-complex formation in the case of reaction of *N*-oxides with quinones also corresponds to the HSAB (hard and soft acids and bases) principle: π-acceptors react more effectively with π-orbitals of the donors (the "soft " center).

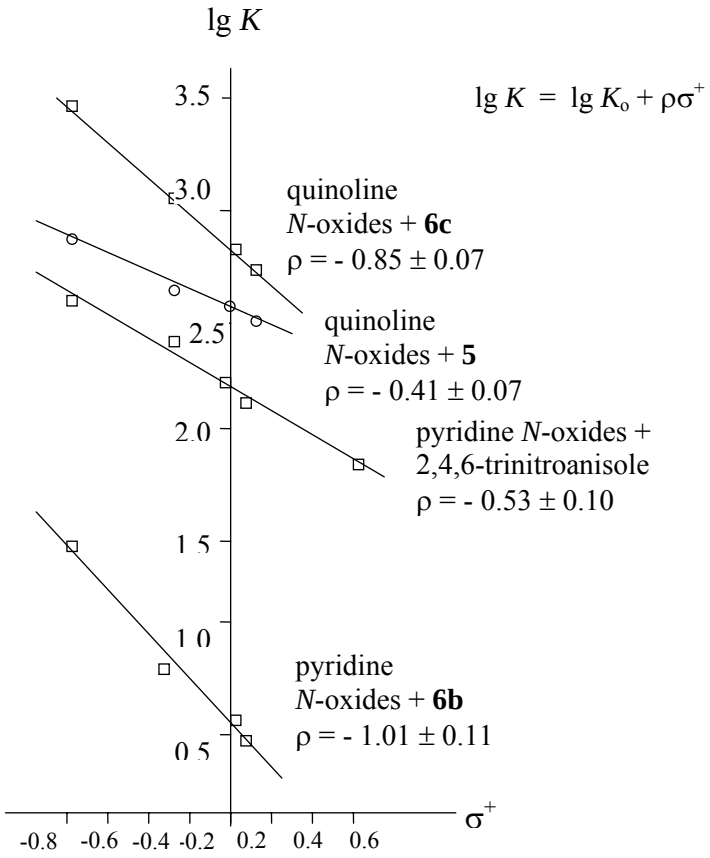


Figure 2. Equilibrium constant of the complex formation reactions between heteroaromatic *N*-oxides and π-acceptors in relation to σ^+ constants of substituents in *N*-oxides

1.2 COMPLEXES WITH V-ACCEPTORS (LEWIS AND BRØNSTED-LOWRY ACIDS)

It has been shown that in most cases *N*-oxides of the pyridine, quinoline and acridine series form stable adducts with BF_3, $CuCl_2$, $ZnCl_2$, HCl with coordination of the acceptor through the oxygen atom of the *N*-oxide group, with the exception of 4-(4'-dimethylaminostyryl)pyridine and 4-(4'-dimethylaminostyryl)quinoline *N*-oxides in which the second molecule of acceptor coordinates to the amino group[9]. For hard acids like BF_3 and H^+ the *N*-oxide – acceptor ratio is 1:1, for the borderline Zn^{2+} is 2:1, and for a soft acid Cu^{2+} it can be both 1:1 and 2:1. The adducts were isolated and characterized by analytical and spectroscopic methods. It should be noted that quinoline and 2-methylquinoline *N*-oxides

also form unstable complexes with $CuCl_2$ as yellow-colored substances, quickly turning into stable species with composition dependent on the donor-acceptor ratio in the solution.

The unusual behavior of 4-nitroquinoline *N*-oxide is worth special attention. It forms two types of stable complexes with BF_3: one of them has composition 1:1, where oxygen atoms of the nitro group are the donor centers, and the other complex has composition 2:1, where NO_2 and *N*-oxide groups simultaneously participate in complex formation. At the same time 4-nitroquinoline *N*-oxide molecular complexes with $AlCl_3$, $AlBr_3$, HCl and HBr are not stable at all. The nitro group is substituted by the halide ion during their formation.

2. NUCLEOPHILIC SUBSTITUTION REACTIONS IN *N*-OXIDES

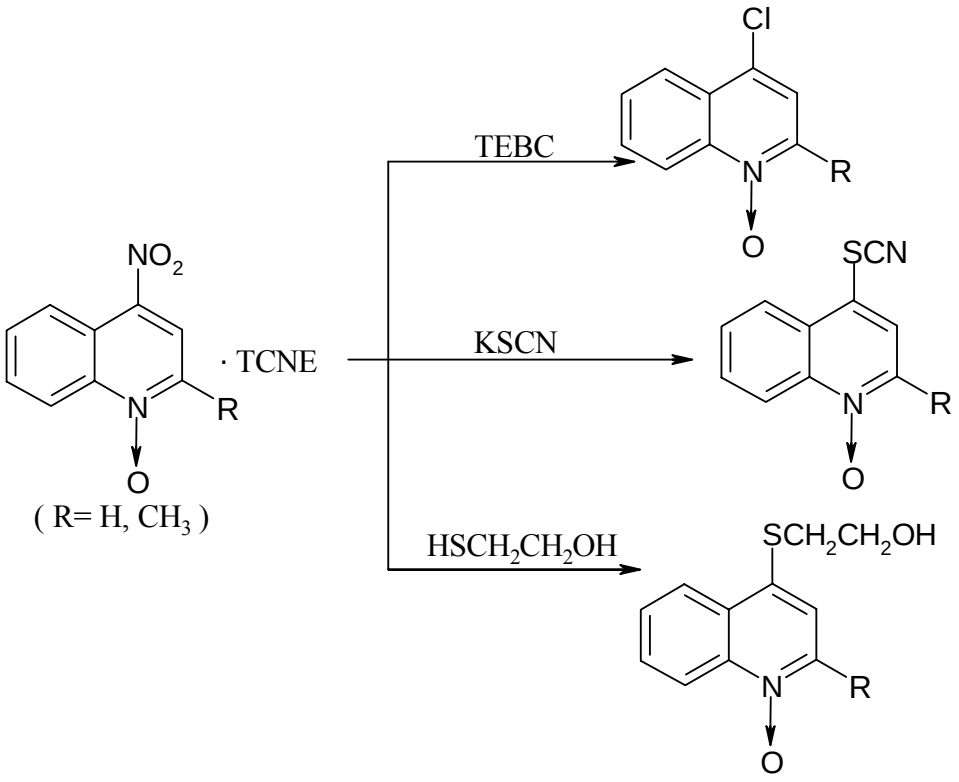
2.1 NITRO GROUP SUBSTITUTION

Nitroquinoline *N*-oxides are the key compounds in the synthesis of substituted quinoline derivatives. Their reactions with strong nucleophiles are smooth, and result in the corresponding *N*-oxide derivatives. However, their reactions with weak nucleophiles either don't take place at all or require harsh conditions and only result in low yields. Thus, the substitution of the nitro group in these compounds by halide ions requires boiling concd HCl or HBr solutions, acetyl halides,[1] or phosphoryl halides.[10] In these cases, the activation of substitution reaction can be explained by the formation of intermediates which are much more electrophilic than the starting *N*-oxides. These methods are not very convenient: they involve refluxing reaction mixtures for a long time, a complicated *N*-oxides isolation procedure, and they lead to deoxygenation and halogenation products in some cases. For example, the yield of 2-bromo-4-nitroquinoline in the reaction of 4-nitroquinoline *N*-oxide with $POBr_3$ in chloroform is 73%.[11]

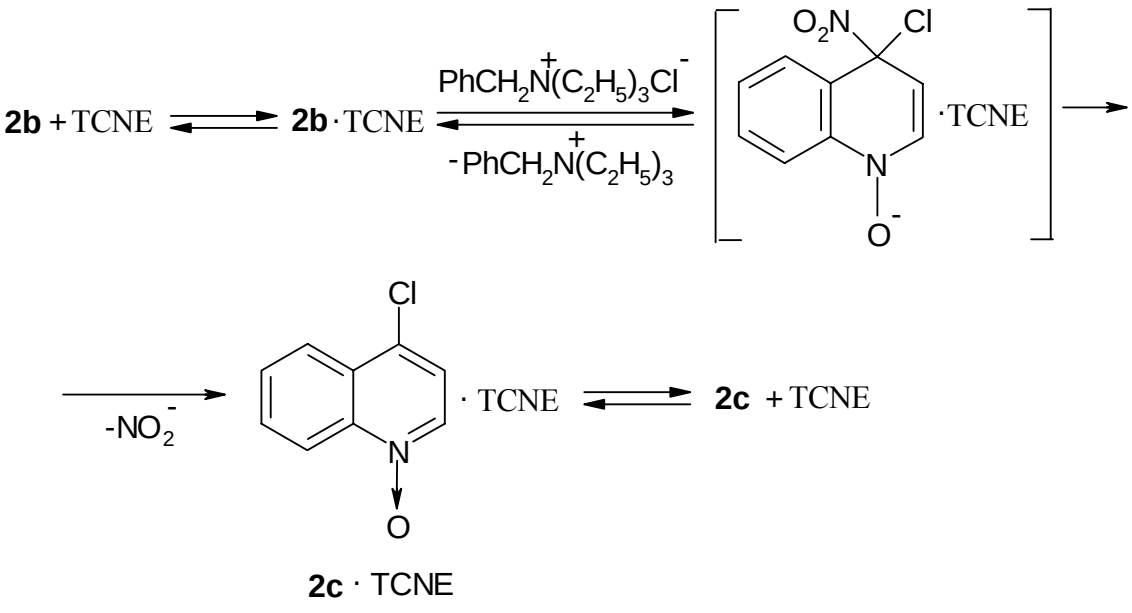
Substitution of the nitro group in 4-nitroquinoline (**2b**) and 2-methyl-4-nitroquinoline, 9-nitroacridine (**4b**) *N*-oxides by chloride, bromide, thiocyanide ions and 2-mercaptoethanol[12] using TCNE as an "external" π-acceptor under mild conditions (room temperature) was successfully achieved.

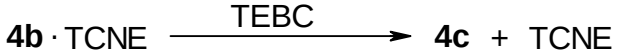
The preparative yields of *N*-oxides in these reactions are 55 – 88%. One can substitute the nitro group by chloride ion in the reaction of *N*-oxide (**2b**) with TCNE, dibenzo-18-crown ether-6 and potassium chloride (ratio 1:2:2:2) in dioxane/acetonitrile mixture (1:1) for 12 h at 35 °C.

Alkali metal iodides and triethylbenzylammonium chloride cannot be used to obtain 4-iodoquinoline *N*-oxide by this method. Addition of these compounds to a solution of (**2b** · TCNE) complex leads to immediate oxidation of iodide ion by tetracyanoethylene to molecular iodine. Chloride, bromide, and thiocyanide ions do not react with TCNE, and their use as nucleophiles does not lead to byproducts of the reaction.



Nucleophilic substitution of NO_2 group by Cl in the MC of 4-nitroquinoline *N*-oxide with TCNE (**2b** · TCNE) and triethylbenzylammonium chloride (TEBC) in a dioxane – acetonitrile mixture (1:1) was studied more closely.





Quantitative and qualitative analyses of the reaction mixtures (based on 4-chloroquinoline *N*-oxide (**2c**)) were performed by HPLC. It should be mentioned that this process is practically unrealizable without TCNE. The yield of *N*-oxide (**2c**) in the system of *N*-oxide (**2b**)- TEBC (ratio 1:4) does not exceed 3% even after 72 h at 40 °C. The formation of MC **2b** · TCNE, existing only in solution, precedes the nucleophilic substitution. A new CTB appears in the electronic spectrum at 432 nm. The MC composition (1:1), formation constant, and extinction quotient (*K* 5.1±0.4 L/mol at 19 °C, lg ε 2.59) were determined by Benesi-Hildebrand method. The complex is easily attacked by the nucleophile (chloride ion) in the second stage of the process (rate-determining). An alternative "arynic" mechanism is also possible. However, this mechanism is unlikely to be realized since isomeric 3-chloroquinoline *N*-oxide formation has not been observed in this process. Indisputable proof in favour of the bimolecular mechanism was obtained by a kinetic study of the reaction of *N*-oxide (**2b**) and TEBC with TCNE. The directly proportional dependence of the starting reaction rate values (ν_H) of this reaction on the TEBC concentration indicates chloride ion participation in the rate-determining step of the process.

The extent of reaction with TCNE changes from 1 to a value close to 0, which is connected with the equilibrium in the MC formation on the first stage of the process and with practically complete binding of *N*-oxide in MC with excess TCNE. The π-acceptor role in the bimolecular substitution mechanism consists of enhancing the *N*-oxide (**2b**) electrophilicity. At the same time, we cannot exclude the possibility of enhancing the stability of anionic σ-complex by TCNE due to extra delocalization of the negative charge in the molecule that decreases the activation energy of the entire process.

In the case of 4-nitroquinoline *N*-oxide (**2b**) we made an attempt to study the substitution of the nitro group by halogen atom, and the activation of heteroaromatic ring by both Lewis acids ($AlCl_3$, SbF_3, $ZnCl_2$, $CuCl_2$) and Br∅nsted-Lowry acids (HCl, HBr, perchloric acids and TFA).

When a strong Lewis acid, BF_3, is added to the reaction mixture in anhydrous acetonitrile at room temperature the reaction with TEBC is complete in 1 h, and when much weaker acids (SbF_3, $CuCl_2$, and $ZnCl_2$) are used, the reaction does not occur. The participation of MC in this reaction is proved by the fact that the solid adduct of 4-nitroquinoline with BF_3 reacts with TEBC at nearly the same rate. Curiously, Br∅nsted-Lowry acids ($HClO_4$ and TFA), which increase the electron density deficit in the heterocycle due to protonation on the oxygen of the *N*-oxide group, cause the transformation rate to be much lower than in the case of BF_3. This fact can be explained by the decrease of chloride anion activity in the presence of proton compounds capable of specific interaction with the anion. However, the use of NH_4Cl and NaCl as chloride ion sources (these compounds are dissolved more easily in acetonitrile containing some water) shows that the strong Br∅nsted-Lowry acids $HClO_4$ and TFA are more effective activators in such systems than Lewis acids (Table 3).

Table 3

Activation of the nucleophilic substitution of the nitro group by chlorine in 4 -nitroquinoline *N*-oxide using π- and v-acceptors (in acetonitrile)[13]

№	Nucleophile	Acceptor	*T* (°C)	Time of reaction [f] (h)	Yield (%)
1	TEBC	TCNE	rt	24	50
2	TEBC	TCNE	rt	A few days	100
3	TEBC	BF_3	rt	1	
4	TEBC	BF_3	65	0.5	
5	TEBC	BF_3 [a]	65	0.5	
6	TEBC	TFA	65	6	
7	TEBC	$HClO_4$	65	8	
8	HCl (concd)	HCl	65	0.5	
9	HCl (concd)	HCl	rt	24	
10	HCl (concd)	HCl [b]	100	1	
11	$AlCl_3$	$AlCl_3$ [c]	65	0.5	
12	$AlCl_3$	$AlCl_3$ [d]	rt	20	90
13	$AlCl_3$	$AlCl_3$ [c]	rt	20	
14	$AlCl_3$	$AlCl_3$ [e]	rt	20	50
16	$AlCl_3 \cdot 6H_2O$	$AlCl_3 \cdot 6H_2O$	65	24	
17	$AlCl_3 \cdot 6H_2O$	BF_3	65	3	
18	$AlCl_3 \cdot 6H_2O$	TFA	65	3	

[a] A solid complex of 4-nitroquinoline *N*-oxide with BF_3 was added into the reaction mixture.

[b] The reaction was performed in concd hydrochloric acid.

[f] Monitoring of the reaction was realized by HPLC. The standard reaction mixture contained 0.1 mmol of 4-nitroquinoline *N*-oxide, a nucleophile, and an acceptor in 0.3 mL of absolute acetonitrile. The reaction time was measured as a period in which 99% of transformation or more is achieved. The molar ratio *N*-oxide/$AlCl_3$ was [c] 1:1, [d] 2:1, [e] 1:2.

Since hydrogen chloride serves as a source of both a proton and a nucleophile (Cl^-) we compared the rate of nitro group substitution reaction in an aprotic solvent like acetonitrile and in concd hydrochloric acid. It was found that in the former case the transformation was complete in 30 min at 65 °C or in 24 h at rt, and in the latter only in 1 h even at 100 °C despite low HCl concentration. Both systems were homogeneous, and we can suggest the following explanation of the above fact: the chloride ion nucleophilicity in concd aqueous hydrochloric acid is lower than in aprotic acetonitrile.

In the case of bromide ion, the rules mentioned above are still in force. However, reaction with concd HBr without a solvent at 100 °C allows substitution of the nitro group by bromine in 30 min, according to HPLC. All attempts to substitute the nitro group in 4-nitroquinoline *N*-oxide by iodide have failed because of an oxidation-reduction reaction with I^- that causes easily producing molecular iodine.

The yield of iodine derivative did not exceed 5% in any of the experiments, according to HPLC.

In aprotic solvents under such conditions, halide ion reactivity increases with basicity ($Cl^- > Br^- > I^-$), which is in agreement with the literature data.[14] In the case of chloride ion in proton solvents, the reaction rate decreases. However, in the case of bromination the increase in the ratio of concd HBr – acetonitrile up to 1:2 not only speeds up the reaction, but also makes the yield of the substitution product higher. This effect can be explained as follows. On the one hand, protic solvents are supposed to decrease halide ion reactivity including bromide ions. On the other hand, when a weaker nucleophile Br^- (compared with Cl^-) in aprotic solvents is used, the reversible stage of the Meisenheimer complex formation obviously limits the substitution process.[14] Here the increase of Br^- concentration by adding hydrobromic acid should shift the equilibrium towards the substitution product. Apparently, the second factor dominates as long as the water content is greater than 10%.

On the basis of this evidence we can conclude that the optimal conditions for activation of nucleophilic substitution by halogen are the reaction of *N*-oxide with a proton accepting anhydrous hydrogen halide in aprotic solvent. In fact, we have proved that if gaseous dry HCl and HBr are passed through a saturated solution of 4-nitroquinoline *N*-oxide in chloroform, the transformation process is complete in 15-30 min with a quantitative yield.[15]

So, the substitution of the nitro group in 4-nitroquinoline *N*-oxide, with activation by strong Lewis and Br∅nsted-Lowry acids, is an efficient method of preparation of 4-chloro- and bromoquinoline *N*-oxides.

Continuing this research we studied the possibility of the activation of nitro group substitution in heteroaromatic *N*-oxides with anhydrous $AlCl_3$. $AlCl_3$ is a strong enough Lewis acid to form molecular complexes with *N*-oxides. Similar to BF_3 it should increase their electrophilicity in reactions with weak nucleophiles. However, aluminium chloride appeared to be both a powerful v-acceptor and a rather effective nucleophilic reagent as a chloride ion source. According to HPLC, heating of equimolar quantities of *N*-oxide (**2b**) and $AlCl_3$ in acetonitrile for 15 min at 65 °C or reacting at rt for 24 h results in formation of 4-chloroquinoline N-oxide (**2c**) in quantitative yields.

Addition of an equimolar quantity of TEBC in the last reaction practically does not affect the reaction rate, and this shows that under these conditions anhydrous $AlCl_3$ is nonetheless an efficient chloride ion source. Halogen-containing Lewis acids like SbF_3, BF_3, $ZnCl_2$, $CuCl_2$, unlike $AlCl_3$ are poor source of halide ions (BF_3), or acceptors ($ZnCl_2$ and $CuCl_2$), or both (SbF_3) under the aforementioned conditions.

On the contrary, the presence of proton-donating compounds capable of specific interaction slows down the substitution.

$$\mathbf{2b}\cdot AlCl_3 \xrightleftharpoons{AlCl_3} \mathbf{2b}\cdot 2AlCl_3$$

This is observed, for example, in reactions where acetonitrile was used instead of methanol, $AlCl_3$ for $AlCl_3 \cdot 6H_2O$, BF_3 for CF_3COOH or $HClO_4$. We also showed that at reducing the ratio *N*-oxide (**2b**) / $AlCl_3$ from 2:1 to 1:2 slows down the process. At the same time the fraction of complex (**8**) is supposed to increase, and in this complex electron density deficit on the aluminium atom (the electron sextet) is compensated to a lower degree due to the competition between the two molecules $AlCl_3$ thereby making it much more difficult to generate the chloride-ion nucleophile particle.

It should be mentioned that such complexes with BF_3 are stable in the solid state and they were isolated preparatively.

Thus, when $AlCl_3$ or hydrogen halides (HCl, HBr) are used, the nucleophilic substitution of *N*-oxide by halogen usually starts with formation of a molecular complex with Lewis or Brønsted-Lowry acids. This is followed by the halogen anion release and this anion in its turn attacks the aromatic ring thus enabling the substitution product formation.

It is necessary to stress the following point: electron density is so much withdrawn by the proton that *N*-oxide hydrochloride (**2b**) cannot be isolated (analogous to the complex with $AlCl_3$). As mentioned before, substitution of the nitro group by halogen takes place very quickly.

1.1 HALOGEN SUBSTITUTION

The lability of the halogen atoms in CTC of *N*-oxides of 4-chloro- and 4-bromopyridine, quinoline and acridine derivatives with π-acceptors is demonstrated in their interaction with the $AgNO_3$ solution in acetonitrile. Immediate precipitation of silver halide is observed. The corresponding *N*-oxides react much slower – over several hours. A detailed study of chlorine substitution in CTC of 4-chloroquinoline *N*-oxide (**2c**) with bromanile by benzoylhydrazines has been performed.[16] (Table 4, method A):

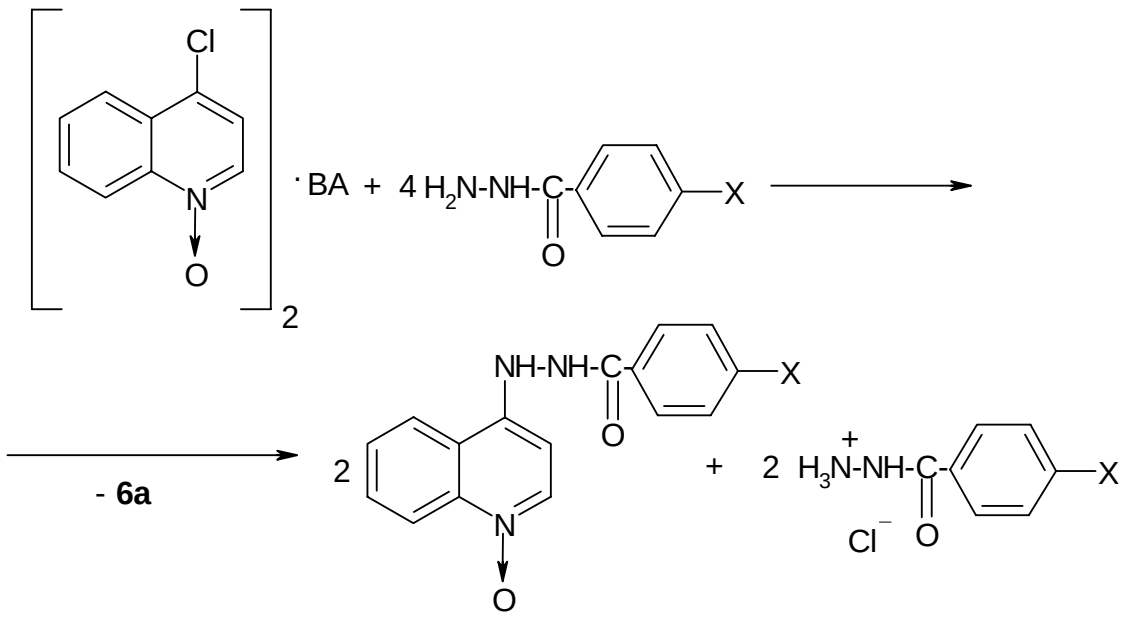


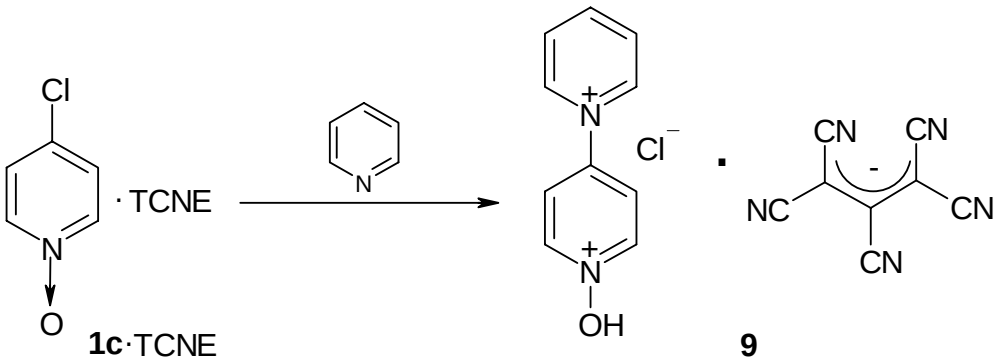
Table 4

CTC $(2\ c)_2 \cdot$ BA and 4-X-substituted benzoylhydrazines reactions

Substituent X	mp (°C)	Method	Yield (%)
NO_2	198–200	A	66
NO_2		B	38
Cl	200–202	A	59
Cl		B	32
H	206–209	A	78
H		B	32
OCH_3	210–212	A	42
OCH_3		B	0

Unlike CTC of nitro substituted *N*-oxides these complexes with BA were isolated in the solid state. They were used in nucleophilic substitution reaction with benzoylhydrazides in dioxane. The CTC reactions with benzoylhydrazides take place under mild conditions (room temperature) in reasonable yields and are completed in 1-2 h (method A). The structure of the substitution products was confirmed by elemental analysis, IR and NMR spectra.[17] Independently we carried out reactions of 4-chloroquinoline *N*-oxide with 4-substituted benzoylhydrazines without BA (Table 4, method B). These processes do not take place if the temperature is under 80 °C, and it is necessary to heat the mixtures for 4 h at 100 °C in dioxane to bring the reactions to completion. However, the reaction mixtures resinify considerably, and *N*-oxides deoxygenate to some extent,[18] which decreases the yield of the substituted *N*-oxides derivatives. It appeared impossible to get methoxy-derivatives by applying method B.

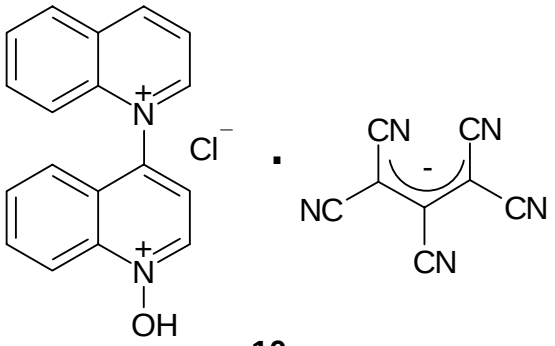
It should be mentioned that the addition of benzoylhydrazides a reaction mixture of *N*-oxide (**2c**) and the acceptor (**6a**) does not result in substitution products. In this case, bromanile (**6a**) is regenerated to tetrabromohydroquinone, and *N*-oxide (**2c**) stays unchanged. The Cl^- substitution processes in *N*-oxide complexes with TCNE in the presence of pyridine, which take place under mild conditions and can serve as other examples of halogen nucleophilic substitution, resulting in quaternary pyridine derivatives.[19] However, unlike the case of the preceding reactions, the products are not isolated directly; they form salts with the TCNE acceptor transformation product – pentacyanopropenide anion. In the case of *N*-oxide (**1c**) and a nucleophile (pyridine), the process is presented by the following scheme:



1c·TCNE **9**

Without TCNE these processes cannot take place. We measured the values of enthalpy and entropy of the cooperative process. They are 2.0±0.3 kJ/mol and 202±9 J/(mol ·K), respectively. So negligible changes of the observed cooperative process rate constant (*K*), which is temperature dependent, can be explained by the equilibrium shift in the first stage of the process (complex formation) towards MC **2c** ·TCNE dissociation. At the same time the low entropy of activation indicates a highly ordered intermediate state (Meisenheimer anionic σ-complex).

Similarly, the interaction of MC quinoline *N*-oxide and TCNE with quinoline takes place, resulting in 4-(*N*-quinoline)-1-hydroxyquinoline chloride pentacyanopropenide (**10**):

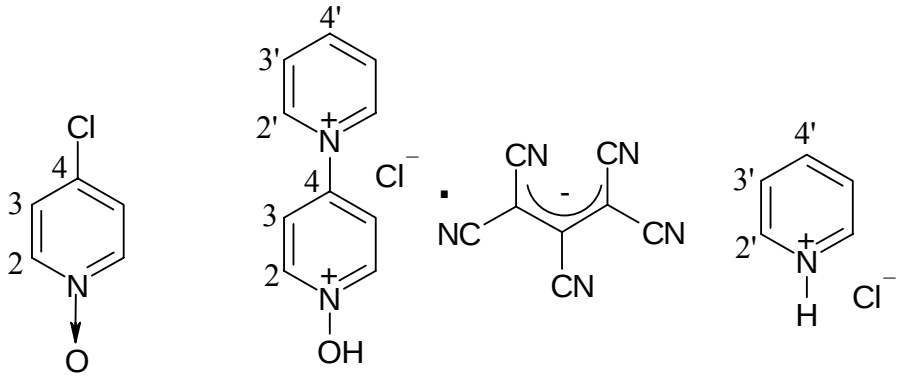


10

1.2 PYRIDINIUM CATION SUBSTITUTION

Quaternary pyridinium and quinolinium salts of *N*-oxides (**9**, **10**) were obtained by the authors. They contain some of the most nucleophilic substituents in position 4 – the pyridinium or the quinolinium cation. Our study of *N*-oxide (**1c**) and compound (**9**) by the ^{13}C NMR method (Table 5) confirmed that the electron deficiency of the *N*-oxide ring of **9** and **10** is higher than that of the starting chloropyridine and chloroquinoline *N*-oxides.

According to the literature data one group of signals in the compound (**9**) spectrum corresponds to the pyridinium cation. The other group is characteristic of the *N*-oxide fragment. It is typical that the C-2 and C-3 signals are slightly shifted downfield due to the general *N*-oxide aromatic system deshielding. This is the result of chlorine atom replacement by pyridinium cation and the formation of a complex with TCNE.



1c **9** **11**

The greatest downfield shift (about 3 ppm) is usually observed for the C-4 atom. Therefore, the salt (**9**) should be more sensitive to nucleophilic attack than the *N*-oxide (**1c**)

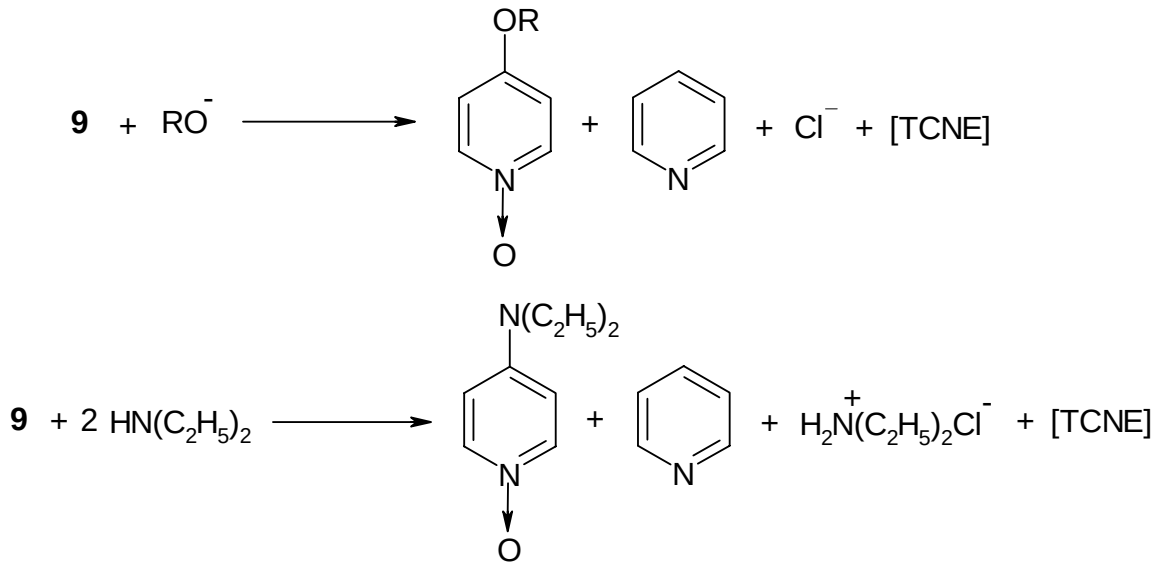
Table 5

^{13}C NMR spectra of N-oxide (**1c**), compound (**9**) and pyridine hydrochloride (**11**)

Compound	Chemical shift (δ, ppm)					
	2 C-2	2 C-3	C-4	2 C-2'	2 C-3'	C-4'
1 c	140.39	127.00	129.88	—	—	—
9*	140.56	127.30	132.84	142.09	127.64	146.80
11*	—	—	—	141.90	127.60	146.90

∗) atoms of the pyridinium cation in the compounds (**9**) and (**11**) are marked with apostrophes

When compound (**9**) is treated with potassium hydroxide, sodium alkoxides, sodium phenoxide or aliphatic amines under mild conditions, 4-substituted pyridine *N*-oxides form:



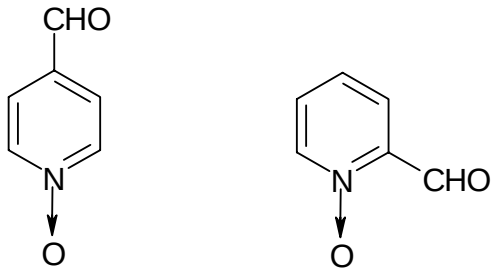
The yields of pyridine *N*-oxide are 70 – 93%. In the case when individual (isolated) *N*-oxide (**1c**) is used these reactions take place under more drastic conditions over a longer period of time. For example, its interaction with morpholine goes to completion only at 135 °C in a sealed tube in 5 h. Besides, under these conditions *N*-oxides are subject to deoxygenation.

It should be mentioned that adding sodium alkoxides or secondary amines directly to the mixture of *N*-oxide and TCNE, but not to compound (**9**), in order to activate the nucleophilic chloride ion substitution does not yield the expected products. The reaction of TCNE with nucleophiles and the formation of tricyanovinyl derivatives like $(NC)_2$ C = C(CN)-X (X=OR, NR_1R_2) are observed, while the *N*-oxide (**1c**)

is recovered unmodified. Using compound (**9**) as an intermediate makes it possible to carry out nucleophilic substitution reactions on the *N*-oxide (**1c**).

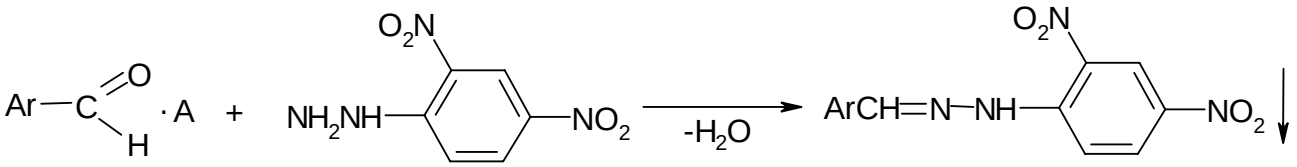
2. REACTIONS OF NUCLEOPHILIC ADDITION OF PYRIDINECARBOXALDEHYDES AND AROMATIC CARBONYL COMPOUNDS WITH *N*-OXIDES

The principle of nucleophilic substitution reactions in the aromatic *N*-oxides series, which we used, was also applied to nucleophilic addition reactions on aromatic carbonyl compounds, including 4-pyridinecarboxaldehyde (**12**) and 2- pyridinecarboxaldehyde (**13**) *N*-oxides.[21]



12 **13**

MC of N-oxides (**12** and **13**) and also substituted benzaldehydes and benzophenones with π-acceptors exist only in solutions. These complexes were studied by NMR and UV spectroscopy. The MC were exposed to a weak nucleophile – 2,4-dinitrophenylhydrazine at room temperature in acetonitrile:



A = **5, 6a-c**

The reactions are complete in 5 – 10 min; hydrazones are formed with high (often quantitative) yields. It is well known that acidic catalysis is usually employed in the process of the formation of 2,4-dinitrophenylhydrazones. Practically the condensation is conducted in sulfuric or hydrochloric acid with a 2,4-dinitrophenylhydrazine solution prepared in advance. The acidic catalysis enhances the electrophilicity of the carbonyl compound, which makes it easier for weak nucleophiles to attack it. We showed that this result can also be obtained by using π-acceptors. It should be noted that the method described in the review has a number of advantages in comparison with other well-known methods. For example, it is more convenient and easier to apply in order to get small amounts of aromatic 2,4-dinitrophenylhydrazones of carbonyl compounds for the purpose of their identification. It is worth notingthat in practice Ad_N reactions of aliphatic aldehydes and ketones do not accelerate in case of π-

acceptor interactions, since these carbonyl compounds form much weaker CTCs contrary to aromatic ones.

CONCLUSIONS

Our research has shown that binding heteroaromatic *N*-oxides into donor- acceptor complexes with π- or v-acceptors enhances their activity towards nucleophilic reagents. This fact proves the possibility of enlarging the synthetic potential of nucleophilic substitution reactions in the chemistry of aromatic heterocycles, and, consequently, of a wider utilization of *N*-oxides and other aromatic compounds.

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REFERENCES

1. E. Ochiai, Aromatic Amine Oxides, Amsterdam, Elsevier, 1967.
2. A. R. Katritzky and J. N. Lam, *Heterocycles*, 1992, **33**, 1011.
3. A. V. Ryzhakov and L. L. Rodina, Sint., Str., Khim. Org. Soedin. Azota, 1991, 11, Ross. Gos. Pedagog. Univ., Leningrad, USSR. (*Chem. Abstr*., 1992, **116**, 214312 r).
4. A. F. Pozharskij, in: Five-membered Aromatic Heterocycles, Zinatne, Riga, 1979.
5. L. L. Rodina and A. V. Ryzhakov, *Heterocycles*, 1995, **40**, 1035.
6. O. O. Alexeeva, L. L. Rodina, A. V. Ryzhakov, and S. M. Korneev, *Zh. Org. Khim*., 1997, **33**, 1395. (*Chem. Abstr*., 1998, **129**, 14889 w).
7. M. E. Peover, *J. Chem. Soc*., 1962, 4540.
8. J. E. Frey, *Appl. Spectroscopy Rev*., 1987, **23**, 247.
9. V. P. Andreev and A. V. Ryzhakov, *Chem. Heterocycl. Comp. Russia*, 1994, 1087. (*Chem. Abstr*., 1995, **122**, 159981 e); V. P. Andreev, E. G. Batocyrenova, A. V. Ryzhakov, and L. L. Rodina, *Chem. Heterocycl. Comp. Russia*, 1998, 1093. (*Chem. Abstr*., 1999, **130**, 325080 x).
10. A. F. Pozharskij, The Theoretical Fundamentals of Heterocyclic Chemistry, Khimiya, Moscow, 1985; E. Ochiai, *J. Org. Chem*., 1953, **18**, 534.
11. M. Hamana, Y. Hoshide, and K. Kaneda, *Yakugaku Zasshi*, 1956, **76,** 1337. (*Chem. Abstr*., 1957, **51**, 6639 c).

12. A. V. Ryzhakov and L. L. Rodina, *Zh. Org. Khim*., 1994, **30**, 1417. (*Chem. Abstr*., 1995, **123**, 255914 b).
13. A. V. Ryzhakov, "Heteroaromatic *N*-oxides in the reactions with electronodeficient compounds", Dissertation (B), Technological University of St. Petersburg, 2000.
14. B. F. Terrier, *Chem. Rev*., 1982, **82**, 77.
15. V. P. Andreev, E. G. Korvachyova, and L. L. Rodina, The Activation of the Nucleophilic Substitution Reaction by Brønsted and Lewis Acids in the Range of Heteroaromatic *N*-Oxides. Book of Abstracts. 11th International Conference of Organic synthesis (ICOS-11) , 1996, Amsterdam, The Netherlands, p.452.
16. A. V. Ryzhakov, O. O. Alexeeva, and L. L. Rodina, *Zh. Org. Khim*., 1994, **30**, 1411. (*Chem. Abstr*., 1995, **123**, 338773 f).
17. O. O. Alexeeva, " Interaction of Aromatic *N*-Oxides with π-Acceptors", Ph. D. Dissertation, University of St.-Petersburg, Russia, 1996.
18. A. V. Ryzhakov and N. R. Elaev, *Chem. Heterocycl. Comp. Russia*, 1987, 1075. (*Chem. Abstr*., 1998, **129**, 54615 c).
19. A. V. Ryzhakov, V. V. Vapirov, and L. L. Rodina, *Zh. Org. Khim*., 1991, **27**, 825. (*Chem. Abstr*., 1992, **116**, 20494 f).
20. L. L. Rodina, A. V. Ryzhakov, and O. O. Alexeeva, *Chem. Heterocycl. Comp. Russia*, 1995, 184. (*Chem. Abstr*., 1995, **123**, 143613 w).
21. A. V. Ryzhakov and L. L. Rodina, Pat. USSR No 1786023. (*Chem. Abstr*., 1993, **119**, P 180639 x).