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ACTIVATION OF NUCLEOPHILIC SUBSTITUTION REACTIONS IN 4-NITROQUINOLINE N-OXIDE BY v-ACCEPTORS

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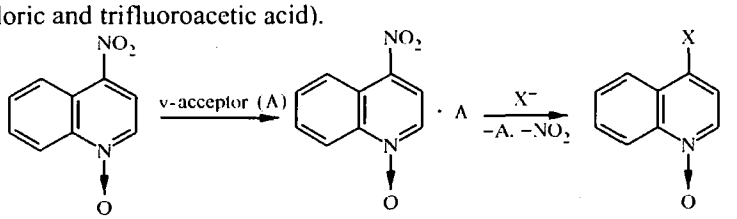
The method of HPLC was used to investigate the influence of temperature, solvent, the nature of the nucleophile, and the type of v-acceptor on the rate of substitution of the nitro group in 4-nitroquinoline N-oxide by atoms of halogens. Convenient methods for the synthesis of 4-halo-substituted quinoline N-oxides under conditions of activation of the reaction by Lewis and Bronsted–Lowry acids are proposed.

Formation of charge transfer complexes is known to proceed, on account of the partial or complete transfer of an electron from the HOMO of the donor to the LFMO of the acceptor, leading to the redistribution of electron density in the reacting molecules. This results in a change of their reactivity, especially in regard to nucleophilic or electrophilic reagents. We first proposed this approach previously to accomplish the reaction between 4-nitroquinoline N-oxide and triethylbenzylammonium chloride (TEBA) in the presence of tetracyanoethylene, capable of forming charge transfer complexes of the π,π-type [1]. The indicated process proceeds readily at room temperature giving 4-chloroquinoline N-oxide (in the absence of tetracyanoethylene, the yield does not exceed 3% even after 72 h at 40°C) in good yield. However, it is of low suitability for the isolation of the reaction product in preparative amounts.

When Bronsted–Lowry acids are used, the electrophilicity of the heteroaromatic ring should be significantly higher than that in the case of the less active π-acceptors as a result of the protonation of the oxygen atom of the N→O group. In fact, we showed [2] that when gaseous dry HCl and HBr are passed through the saturated solution of 4-nitroquinoline N-oxide in chloroform, the conversion is completed at room temperature with the yield close to quantitative in 15-30 min.

In the given work, the more detailed investigation of the reaction of substitution of the nitro group by halogen atoms was attempted using the example of 4-nitroquinoline N-oxide under conditions of activation of the heteroaromatic nucleus both by Lewis acids (BF_3, $AlCl_3$, SbF_3, and $ZnCl_2$) and by Bronsted–Lowry acids (hydrohalic acids, perchloric and trifluoroacetic acid).



X = Cl, Br, I; A = BF_3, $AlCl_3$, SbF_5, $ZnCl_2$, H^+

It can be seen from Table 1 that the reaction with TEBA in the presence of the strong Lewis acids BF_3 and $AlCl_3$ in dry acetonitrile at room temperature is completed in 1 h or 24 h correspondingly, whereas the utilization of the much weaker acids SbF_3 and $ZnCl_2$ [3] for this purpose in of low effectiveness. It is interesting that in the case when the acceptors (proton sources) are Bronsted–Lowry acids ($HClO_4$ and CF_3CO_2H), which should increase the deficit of electron density still more in the heterocycle due to protonation at the oxygen atom of the N→O

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TABLE 1. Activation of Nucleophilic Substitution of the Nitro Group by Halogen Atoms in 4-Nitroquinoline N-Oxide by ν-Acceptors

N	Nucleophile	Acceptor	Solvent	T, °C	Yield, %					Note
					30 min	60 min	120 min	180 min	240 min	
1	2	3	4	5	6	7	8	9	10	11
1	Triethylbenzyl-ammonium chloride	BF_3	CH_3CN	65	>99					
2	"	"	"	Room temperature	80	99				
3	"	"	Chloroform	Room temperature	30		45		50	
4	"	$AlCl_3$	CH_3CN	Room temperature		25				24 h, 99%
5	"	SbF_3	CH_3CN	Room temperature			3			
6	"	$ZnCl_2$	"	Room temperature						24 h, 0%
7	"	CF_3CO_2H	"	65	70	80	90	90	95	10 min, 45 %
8	"	$HClO_4$	"	65	65	75	80			10 min, 60 %
9	NH_4Cl	BF_3	"	65	20	35	55			
10	"	SbF_3	"	65		<1	1			
11	"	$HClO_4$	"	65	45	65	80			
12	"	"	CH_3CN–H_2O, 92:8	65	50	65	75	80	95	6 h, >99%
13	"	"	"	Room temperature				2		24 h, 15%
14	"	"	CH_3CN–H_2O, 84:16	65	20	35	50	55	65	6 h, 70%
15	"	CF_3CO_2H	CH_3CN–H_20, 92:8	65	25	45		85		
16	"	$HClO_4$	Dioxane	65	50	70	90	>99		
17	"	"	96% ethanol	65	20	40		70	75	
18	NaCl	"	CH_3CN	65	20	35		50	55	

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11
19	"	"	CH_3-CH_2O, 84:16	65	50	55	60			10 min, 20%
20	"	"	"	Room temperature					5	24 h, 10%
21	HCl (conc.)	HCl	CH_3CN	65	>99					
22	HCl (conc.)	"		Room temperature	50	65				10 min, 30%
23	HCl (conc.)	"	None	100		>99				5 min, 25% 10 min, 50% 15 min, 65%
24	Trimethylhexadecylammonium bromide	BF_3	"	65	30		40		45	10 min, 25%
25	"	"	"	Room temperature	10		10		10	10 min, 10% 24 h, 10%
26	Tetrabutylammonium bromide	$HClO_4$	CH_3CN	65	30		35		35	
27	"	BF_3	Dioxane	100		30	35	40		
28	HBr (conc.)	HBr	CH_3CN	65	35		35		35	
29	HBr (conc.)	"	Dioxane	100	45	30	20	10		10 min, 40%
30	HBr (conc.) 0.15 ml	"	CH_3CN 0.15 ml	65	40	55		60	70	10 min, 10%
31	HBr (conc.) 0.1 ml	"	CH_3CN 0.2 ml	65	50	65	70	70	70	
32	HBr (conc.)	"	None	100	95	95			95	10 min, 35%
33	Triethylbenzylammonium iodide	$HClO_4$	CH_3CN	65					1	
34	"	CF_3CO_2H	"	65		3				
35	"	"	Dioxane	100		5				

*The standard reaction mixture contains, in each case, 0.1 mmol of 4-nitroquinoline N-oxide and the nucleophile, 0.02 ml of solution of the acceptor (BF_3 etherate, trifluoroacetic acid, perchloric acid, or hydrohalic acid) or 0.1 mmole of SbF_3 ($AlCl_3$ or $ZnCl_2$), and 0.3 ml of the solvent. In experiments with a change in the proportion of hydrohalic acid–solvent, their total volume comprised 0.3 ml.

group, the rate of conversion is significantly lower than in the case of BF_3. This fact can be explained by suggestion that the activity of the chlorine anion should decrease in the presence of protonic compounds capable of specific interaction with it.

However, the application of NH_4Cl and NaCl , which have better solubility in acetonitrile containing a small amount of water, as the source of the chloride ion, indicates that the strong Bronsted–Lowry acids $HClO_4$ and CF_3CO_2H are more effective as activators in such systems by comparison with Lewis acids (Table 1).

Since hydrogen chloride is simultaneously a source of protons and nucleophile (Cl^-), we compared the rate of substitution of the nitro group in the aprotic solvent acetonitrile and in concentrated HCl. In the first case, the conversion was completed in 30 min at 65°C or in 24 h at room temperature and, in the second case, only after 1 h in spite of the high concentration of HCl even at 100°C. Both systems are homogeneous and therefore we are also inclined to explain that fact by the lower nucleophilicity of the chloride ion in concentrated aqueous hydrochloric acid in comparison with the aprotic acetonitrile. Nucleophilic substitution in the aromatic series is usually accomplished according to the bimolecular mechanism *via* the formation of Meisenheimer complexes [4]. Delocalization of negative charge thereby occurs in the transition state in comparison with the initial compounds. Therefore, protonic solvents (water, ethanol), which are better in the solvation of small nucleophiles such as Cl^-, should slow down the reaction rate, and aprotic solvents (chloroform, acetonitrile, dioxane), which are better in the solvation of the transition state, should accelerate the reaction.

On the basis of the data obtained (Table 1), the conclusion can be made that the reaction of concentrated HCl with 4-nitroquinoline N-oxide in aprotic solvents (acetonitrile, dioxane) is a very convenient method for the synthesis of 4-chloroquinoline N-oxide. The conversion is accomplished in quantitative yield even at room temperature in 24 h.

In the case of the use of bromide ion sources, the regularities noted above are generally preserved, but the reaction proceeds at a much lower rate. The reaction with concentrated HBr in acetonitrile at 65°C allows the isolation of 4-bromoquinoline N-oxide with the yield of 35% only. The increase of the temperature to 100°C allows the reaction to be accomplished by 50% in 10 min, but further heating leads to competing processes (particularly hydrolysis [5]), and the increase of the time beyond 30 min only lowers the yield of the desired N-oxide. However, the performing of the reaction with concentrated HBr without a solvent at 100°C for 30 min allows the almost quantitative substitution of the nitro group by bromine according to the HPLC data.

Attempts to substitute the nitro group in 4-nitroquinoline N-oxide by iodine were unsuccessful due to oxidation–reduction reactions, readily proceeding with the participation of I^-, with the formation of molecular iodine. According to the HPLC data, the yield of the iododerivative did not exceed 5% in any of the experiments.

Therefore, we showed that the substitution of the nitro group in 4-nitroquinoline N-oxide by halogen atoms under conditions of activation by strong Lewis and Bronsted–Lowry acids is a convenient method for the synthesis of N-oxides of 4-chloro- and bromoquinolines.

The reactivity of the halide ions in aprotic solvents in the conditions under consideration increases with the increase in their basicity ($Cl^- > Br^- > I^-$), which corresponds with published data [4]. In the case of the chloride ion, the addition of protic solvents slows down the reaction rate. However, in the bromination, the increase in the ratio of concentrated HBr–acetonitrile to 1:2 increases not only the reaction rate, but also the yield of the substitution product. Such an effect can be explained as follows. On the one hand, as was shown previously, protonic solvents should decrease the reactivity of halide ions including bromide ions. On the other hand, when the nucleophile Br^-, which is weaker in aprotic solvents by comparison with the Cl^-, is used, the reversible stage of formation of the Meisenheimer complex probably limits the substitution process [4]. The increase in the concentration of Br^- on the addition of hydrobromic acid should thereby shift the equilibrium toward the formation of the substitution product. The second factor is apparently more significant as long as the water content does not reach ~10%.

As was also expected, an increase in the temperature not only accelerates the halogenation reaction, but also increases the probability of secondary processes, particularly hydrolysis (Table 1, experiment 29). When HBr is substituted by the aqueous solution of $HClO_4$ under indicated conditions, a substance with the same retention time is formed according to the data of HPLC, but the reaction with water does not proceed in the absence of acids.

The aim of further work is to realize the principle of the activation of v-acceptors in other nucleophilic substitution reactions in the series of different heterocyclic compounds both with and without the N-oxide function.

EXPERIMENTAL

The monitoring of the investigated conversions of 4-nitroquinoline N-oxide was accomplished by the HPLC control of accumulation of the reaction products. Aliquots (0.05 ml) of reaction mixtures were transferred to test tubes containing 0.45 ml of 3% solution of trimethylamine in ethanol. Conditions of chromatographic analysis were follows: the column with Separon SGX C18 (3 × 150 mm), the mobile phase 84:16 mixture of acetonitrile-water, the eluent flow rate of 0.2 ml/min, the ultraviolet LCD 2040 detector (λ = 335 nm), the CI 100A integrator, the HPP 5001 high-pressure pump, and the sample volume of 0.5 μl.

4-Chloroquinoline N-Oxide Hydrochloride. A. The mixture of 0.19 g (1 mmol) of 4-nitroquinoline N-oxide and 0.5 ml of concentrated HCl is heated at 100°C for 10 min. The reaction mixture is evaporated to dryness in vacuum. A yellow-orange powder is obtained with the yield of 0.203 g (94%). The substance is dissolved by heating to boiling in the minimal amount of butan-1-ol. The crystals are precipitated with ether and dried in air, mp 151-152°C [2].

4-Bromoquinoline N-Oxide Hydrobromide. The compound is synthesized analogously, but applying 1 ml of concentrated HBr, and the reaction mixture is heated at 100°C for 30-40 min with the monitoring by HPLC. The yield is 92%, mp 154-156°C.

B. The mixture of 0.19 g (1 mmol) of 4-nitroquinoline N-oxide, 0.2 ml of concentrated HCl, and 3 ml of acetonitrile is heated at 65°C for 30-40 min, or is left at room temperature for 24 h. At the end of the reaction, monitored by HPLC, the solution is evaporated to dryness in vacuum. The hydrochloride is isolated as described in the experiment A. The yield is 90-95%.

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