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OXIDATIVE CHLORINATION OF ACETANILIDES BY METAL CHLORIDES - HYDROGEN PEROXIDE IN ACID - AQUEOUS MEDIUM SYSTEMS

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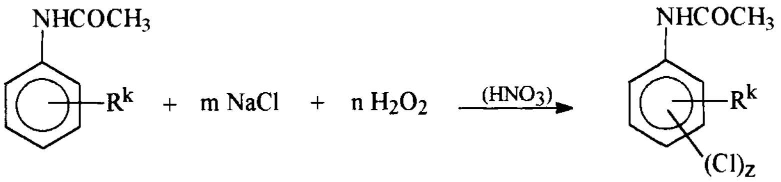
Abstract: The reaction of chlorination of acetanilides by systems: metal chlorides - hydrogen peroxide in acid-water medium gives the chlorosubstituted acetanilides in good yield.

Chloroderivatives of acetanilides can be obtained efficiently by many different methods [1-11]. The aim of the presented studies was to ascertain whether by means of metal chloride (MCl_x) - hydrogen peroxide - acid system subjected to an examination in our laboratory [12] it would be possible to introduce chlorine into the aromatic ring of acetanilide (scheme 1).



Scheme 1

The investigation, which was carried out to establish the influence of substituents on the reaction of chlorination of acetanilides by means of the system

Table 1. Chlorination of acetanilides by HNO_3 -NaCl - H_2O_2 system in aqueous medium[a]

No.	Substrate	Products (%)	X [%]	Y [h]	Z [°C]
1	2-methylacetanilide	4-chloro-2-methylacetanilide (82) 2,4-dichloro-6-methylacetanilide (18)	59	6	15
2	3-chloroacetanilide	3,4-dichloroacetanilide (18) 2,5-dichloroacetanilide (76) 2,4,5-trichloroacetanilide (6)	29	7	25
3	2,5-dimethylacetanilide	4-chloro-2,5-dimethylacetanilide (97) 2,4-dichloro-3,6-dimethylacetanilide (3)	41	8	15
4	2-nitroacetanilide	4-chloro-2-nitroacetanilide (28) 2,4-dichloro-6-nitroacetanilide (72)	91	1,5	50
5	3-nitroacetanilide	2-chloro-5-nitroacetanilide (59) 2,4-dichloro-5-nitroacatanilide (39) 2,4,6-trichloro-5-nitroacetanilide (2)	83	5	50
6	4-nitroacatanilide	2-chloro-4-nitroacetanilide (32) 2,6-dichloro-4-nitroacatanilide (68)	88	2	50
7	4-methoxyacetanilide	2-chloro-4-methoxyacetanilide (67) 2,6-dichloro-4-methoxyacetanilide (33)	44	6	15

where:

X - substrate conversion Y - reaction time Z - reaction temperature

[a] mol ratio $[HNO_3]:[NaCl]:[H_2O_2]:[Ar]$ (10:10:7:1) Ar - acetanilide

under examination, revealed that the acetanilides containing electron acceptor substituents undergo chlorination with good yield (Table 1).

During the process of acetanilide chlorination with such donor substituents carried out at the temperature of 50°C, a lower degree of substrate conversion (8-17%) was found. As far as reaction products are concerned, a contribution of chlorine derivatives of acetanilides was equal to several per cent (generally below 5%). Free amines were also identified. This fact indicates, that the rate of hydrogen peroxide decomposition at this temperature is higher than the rate of chlorination or oxidation reaction.

Table 2. Chlorination of acetanilide by system HNO_3 -NaCl - H_2O_2 in aqueous medium[b, c]

No.	molal ratio				substrate conversion [%]	A	B	C	D
	HNO_3	NaCl	H_2O_2	Ar					
1	10	10	10	1	33	1	88	11	
2	20	20	20	1	47	2	61	37	
3	30	30	10	1	62	2	45	52	1
4	40	40	10	1	79	2	34	62	2
5	40	40	20	1	83	2	60	36	2
6	40	40	30	1	85	2	56	39	3
7	40	40	40	1	86	2	55	41	2
8	10	10	20	1	30	1	90	9	
9	10	10	30	1	24		93	7	
10	10	10	40	1	17		97	3	
11	20	20	40	1	44	2	73	25	
12	40	10	40	1	46	2	85	13	
13	40	30	40	1	73	2	89	9	

where: Ar - acetanilide

A - 2-chloroacetanilide C - 2,4-dichloroacetanilide

B - 4-chloroacetanilide D - 2,4,6-trichloroacetanilide

[b] reaction temperature - 20±0,2°C [c] reaction time - 1,5 h

Examinations for optimization were carried out for NaCl-H_2O_2-HNO_3 system by means of acetanilide chlorination keeping a constant concentration of that compound for all samples (Table 2).

Chlorinating systems were also subjected to tests with the use of other metal chlorides and a variety of acids. Syntheses were done in two aspects:

- efficiency of various metal chlorides (MCl_x) was tested in chlorination reaction with introduction of constant amount of nitric acid in a way to fulfill the following condition $[H^+] = [Cl^-]$,
- efficiency of various acids (H_yR) was also tested with the same amount of NaCl just to fulfill the condition $[H^+] = [Cl^-]$ (Table 4).

Table 3. Chlorination of acetanilide by systems
$HNO_3 - MCl_x - H_2O_2$ in aqueous medium[a]

No.	metal chloride (MCl_x)	reaction time [h]	reaction temp. [°C]	substrate conversion [%]	product composition [%]				
					A	B	C	D	E
1	LiCl	2,5	20	81	6	30	59	5	
		1,5	50	82	1	16	75	8	
2	NaCl	2,5	20	80	5	32	58	5	
		1,5	50	81	1	18	73	8	
3	KCl	2,5	20	73	4	37	51	8	
		1,5	50	73	1	22	69	8	
4	$AlCl_3$	2,5	20	76	4	37	51	8	
		1,5	50	78	1	23	69	7	
6	$CoCl_2$	2,5	20	56	4	39	51	4	2
		3,0	50	69	1	10	75	9	5
7	$MnCl_2$	2,5	20	60	3	36	56	4	1
		3,0	50	70	1	8	78	10	3
8	$NiCl_2$	2,5	20	64	3	36	50	9	2
		3,0	50	71	2	17	72	7	2
9	$CuCl_2$	2,5	20	48	6	33	45	14	2
		3,0	50	29	5	27	38	21	9
10	$ZnCl_2$	2,5	20	47	1	65	33	1	
		3,0	50	64	1	26	71	2	
12	$FeCl_3$	2,5	20	39	3	26	52	16	3
		3,0	50	26	2	16	49	23	10

where:

A - 2-chloroacetanilide C - 2,4-dichloroacetanilide E - oxidation products

B - 4-chloroacetanilide D - 2,4,6-trichloroacetanilide Ar - acetanilide

[a] mol ratio $[HNO_3]:[x*Cl^-]:[H_2O_2]:[Ar]$ - (10:10:7:1)

Table 4. Chlorination of acetanilide by systems: H_yR -NaCl - H_2O_2 in aqueous medium[a]

No.	acid (H_yR)	reaction time [h]	reaction temp. [°C]	substrate conversion [%]	product composition [%]			
					A	B	C	D
1	$HClO_4$	2,5	20	77	4	36	57	3
		1,5	50	80	2	23	69	6
2	H_2SO_4	2,5	20	70	3	39	56	2
		2,0	50	73	1	36	60	3
3	$CHCl_2$-COOH	2,5	20	38	3	47	49	1
		3,0	50	42	3	34	61	2
4	H-COOH	2,5	20	23		46	54	
		4,0	50	19	1	7	92	
5	HOOC-COOH	2,5	20	16		73	27	
		1,5	50	19		67	31	2

where:

A - 2-chloroacetanilide C - 2,4-dichloroacetanilide

B - 4-chloroacetanilide D - 2,4,6-trichloroacetanilide

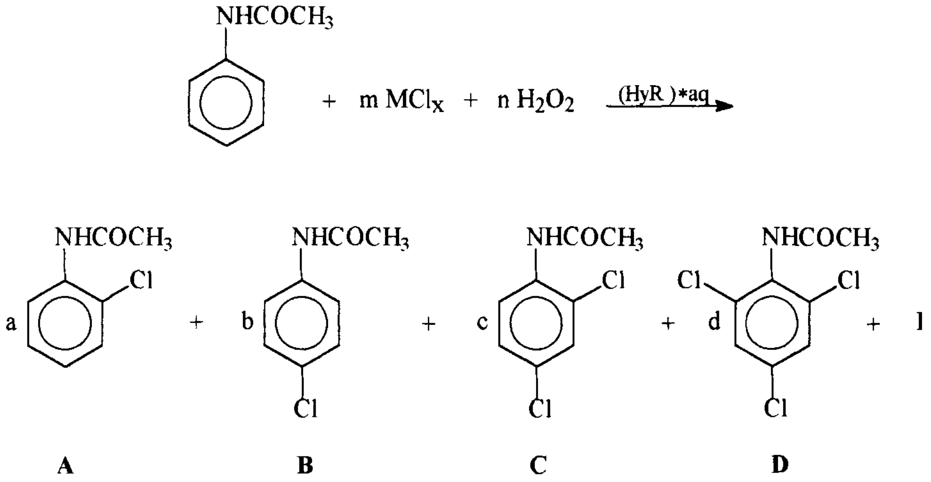
[a] mol ratio $[H_yR]:[NaCl]:[H_2O_2]:[Ar]$ - (10:10:7:1) Ar - acetanilide

Tests concerning the influence of the type of chloride and acid were carried out on a selected acetanilide system (scheme 2).

where:

MCl_x - LiCl, NaCl, KCl, $CaCl_2$, $NiCl_2$, $CoCl_2$, $MnCl_2$, $CuCl_2$, $ZnCl_2$, $AlCl_3$, $FeCl_3$
H_yR - HNO_3, H_2SO_4, $HClO_4$, CH_2Cl-COOH, H-COOH, HOOC-COOH
A,B,C,D,E - reaction chloroproducts and a,b,c,d,m,n - respective coefficients

It was determined, that the degree of substrate conversion and fractions of particular chloride products for the systems in which LiCl, NaCl, KCl, $AlCl_3$ were used, gave comparable results. The increase in temperature had no significant influence on the degree of conversion. For systems containing $CuCl_2$ or $FeCl_3$, chlorination reaction resulted in much lower efficiency, giving considerable fractions of oxidation products. Increase in reaction temperature caused decrease in substrate conversion and increase in fraction of oxidation products.



Scheme 2

The remaining systems studies gave the mixtures of chloride products with nearing composition to that of the first group, which was used in the chlorinating system. In this case however, the chlorination resulted in much lower conversion of substrate.

Mechanism of chlorination with the systems of such composition is unknown. Simplifying the main reactions, it would be possible to reduce our $H_yR\text{-}MCl_x\text{-}H_2O_2$ chlorinating systems to the form of $HCl\text{-}H_2O_2$.

Kinetic aspects of changes occurring within that system have not been fully explained. It is generally accepted, that the system studied consists of series of reactions (1) - (3) given below [13,14,15]:

$$H^+ + Cl^- + H_2O_2 \longrightarrow HOCl + H_2O \qquad (1)$$

$$HOCl + H^+ + Cl^- \rightleftharpoons Cl_2 + H_2O \qquad (2)$$

$$H_2O_2 + HOCl \longrightarrow O_2 + H_2O + H^+ + Cl^- \qquad (3)$$

A significant contribution of H_2O_2 conversion is caused by reaction (4) and (5) with molecular chlorine [16]:

$$Cl_2 + H_2O_2 \rightleftharpoons H^+ + Cl^- + HOOCl \qquad (4)$$

$$HOOCl \longrightarrow O_2 + H^+ + Cl^- \qquad (5)$$

The molecular chlorine formed undergoes partial complexing reaction under the conditions of high chloride concentration (6) [17,18]:

$$Cl_2 + Cl^- \rightleftarrows Cl_3^- \tag{6}$$

A significant quantity, which controls the direction of the changes, so called "steady state function", is defined as (7) [19]:

$$R = \frac{[Cl_2]}{[H^+]^2[Cl^-]^2} \tag{7}$$

and its measure is constant in a wide range of hydrochloric acid concentrations [12,20]. The course of reaction *via* radicals is probable, however it has not been proved [20,21]. Chlorinating systems based on such chlorides as: $CuCl_2$, $MnCl_2$, $CoCl_2$, $FeCl_3$ may induce radicals such as: $OH^\bullet$ or $HO_2^\bullet$, whose presence in the reaction environment may lead to formation of reactive chlorinating species like: $Cl_2^{-\bullet}$, $Cl^\bullet$ [22]. This system in the light of mechanism and reaction kinetics is complex due to the presence of several potentially possible chlorinating factors, such as: HOCl, Cl_2, HOOCl, Cl_3^-, $H_2O{*}Cl^+$, Cl^+ or even $Cl^\bullet$ or $Cl_2^{-\bullet}$.

Experimental part

A solution of nitric acid, into which 0.01 mole of acetanilide and 0.1 mole of NaCl were introduced, was put into a thermostatic reactor equipped with thermometer, stirrer, and reflux condenser. The amounts of chloride and acid were added in such a way that mole proportion $[H^+]/[Cl^-]=1$. After complete acetanilide dissolution, 7 cm^3 of concentrated (d=1.1110 g/cm^3) 29.5% H_2O_2 were added. The reaction was done using times and at temperatures given in Table 1. The amount of water added with the acid was adjusted in such a way, that the final volume of the reaction mixtures amounted to 51.5 cm^3. After lapse of the time needed the solution was neutralized with 3 M NaOH to pH $\in$ (6.7 - 7.3). The deposit formed was then subjected to filtration, dried to a constant mass and finally analysed. The obtained results were listed in Table 1. Optimization tests were carried out in analogous conditions to those described above. The obtained results were summarized in Table 2. Examinations concerning the influence of the kind of chlorides used in chlorination reaction were done in the same manner as given above, except that chlorides were added in such quantity, that the concentration of Cl^- ion was identical for each system. After lapse of required time, the reaction mixture was neutralized with 3 M NaOH, for systems containning: $FeCl_3$ and $AlCl_3$; to pH $\in$ (4.4 - 4.8); for $CuCl_2$ to pH $\in$ (5.8 - 6.0) and to pH $\in$ (6.7 - 7.3) for the remaining chlorides. The deposit formed was subjected to filtration, dried to a constant mass and then analysed. The obtained results are listed in Table 3. Comparative examinations of acid efficiency were also done in analogous conditions using such quantities of acid, that similar concentrations of $[H^+]$ were maintained. The reaction was run within the period of 180 minutes at the temperature of 20±0.2°C. Next, the solution underwent neutralization with 3 M NaOH to pH ∈ (6.8 - 7.2). The obtained results are listed in Table 4. The following compounds were used in present study:

a) acetanilides: following acetanilides of a.p. grade were used: acetanilide, 2-methylacetanilide, 2-nitroacetanilide, 4-nitroacetanilide, etc. (Fluka AG Co.), acetanilide (Aldrich Germany),

b) metal chlorides: chlorides of a.p. grade were applied in the following crystaline forms, which were dried before use: $LiCl*H_2O$ (Aldrich Germany) - dried at the temperature of 105°C; NaCl - dried at temperature of 200°C; KCl (Aldrich Germany) - dried at the temperature 105°C; $MgCl_2*6H_2O$ (Aldrich Germany) - dried in desiccator at room temperature; $CuCl_2$ (Merck) - dried at the temperature 200°C, then dealkalized by dry CO_2, which had been removed in a stream of dry air before use; $CoCl_2$ (Aldrich Germany) - dried at 110°C; $MnCl*2H_2O$ (Merck) - dried in desiccator; $ZnCl_2$ (Merck) - dried in desiccator; $CuCl_2*H_2O$ (Merck) dried in desiccator; $AlCl_3*6H_2O$ (Merck) dried in desiccator; $FeCl_3*6H_2O$ (Merck) dried in desiccator.

Chloride content had been checked argentometrically before it was used in synthesis. In the case when the content of determined chlorides was different from that of the theoretical one (0.3%), a given MCl_x was subjected to repeated crystallization until required Cl^- level was reached. Concentration of hydrogen peroxide was determined manganometrically. The following reagents were also used: acids of a.p. grade: nitric acid (d=1.3825 g/cm^3) (Aldrich Germany); perchloric acid (d=1.5350 g/cm^3) (Aldrich Germany); dichloroacetic acid (d=1.5630 g/cm^3) (Aldrich Germany); formic acid (d=1.0960 g/cm^3) (Merck); oxalic acid (Merck); hydrogen peroxide (d=1.1110 g/cm^3) 29.5 - 32.0% of a.p. grade (Atochem France). Qualitative and quantitative analyses were done by HPLC method (Merck-Hitachi with UV (L-4250) detector; λ = 254 and 286 nm, thermostat L-5025; chromatographic column: lenght 125 mm, ϕ = 4 mm; packing - Hypersil (Shandon) ODS (C-18 phase), 5 μm; eluent: MeOH - H_2O 7:3 flow rate 2 cm^3/min.; pressure 210 bar and GC method (Hewlett Packard HP 5890 series II); detector ECD, capillary column: HP-1, ϕ = 0,32 mm, lenght 30m, temp. 20 - 120°C (15°C/min.) 120-240°C (10°C/min.). Determination was done by use of external standard method.

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