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NOVEL ORTHOHALOGENATION REACTION. SYNTHESIS OF ORTHOCHLOROARYLAMINES FROM NITROARENES.

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Abstract: Thionyl chloride reacts with N-phenylbenzo and N-phenylacetohydroxamic acids at low temperatures to give ortho-chloroanilide derivatives in good yield.

Thionyl chloride reacts with aldoximes and ketoximes to give the corresponding acid amides by the well known Beckmann rearrangement reaction.[1] Similar reaction of thionyl chloride with hydroxamic acids are also known. Benzohydroxamic acid on heating with thionyl chloride gives phenyl isocyanate (Lossen rearrangement).[2] Böshagen[3] showed the formation of mixed anhydride of salicylohydroxamic acid and sulphurous acid by the reaction of thionyl chloride and the enol form of salicylohydroxamic acid.

We now report the reaction of thionyl chloride with N-phenylbenzohydroxamic acid and N-phenyl acetohydroxamic acid derivatives (**1**) to give exclusively the 2-chlorobenzanilide and 2-chloroacetanilide derivatives (**2**) in good yield. Since N-phenyl benzohydroxamic acids and N-phenyl acetohydroxamic acids are prepared from nitrobenzene and its substituted derivatives by reduction to hydroxylamines followed by benzoylation or acetylation: and the resulting 2-chlorobenzanilides and acetanilides (**2**) can be readily hydrolysed to the corresponding 2-chloroarylamines, the overall reaction amounts to the synthesis of orthochloroarylamines from nitroarenes.

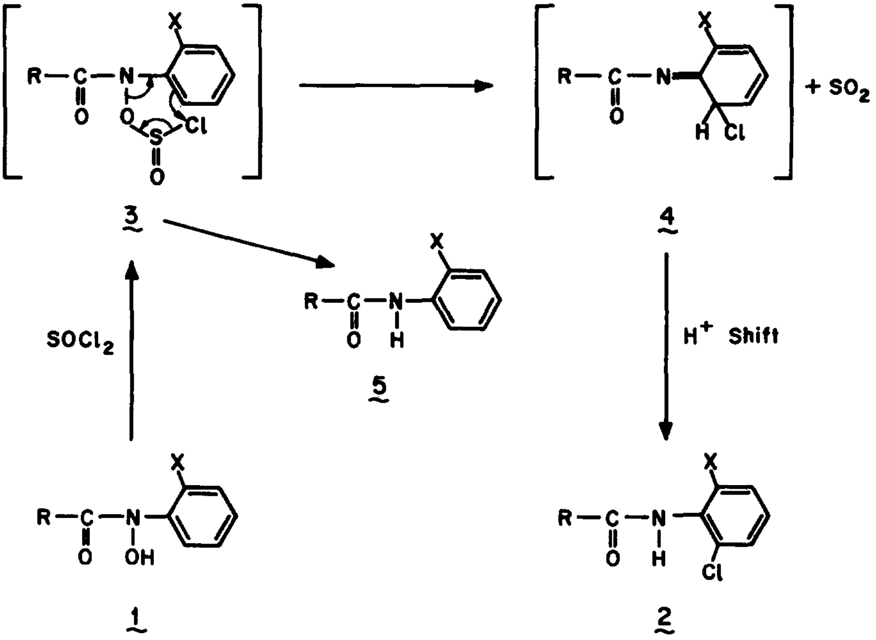
The N-benzo and N-acetohydroxamic acids were prepared by standard methods.[4,5] In a typical experiment, a solution of thionyl chloride (12 mmol, 1.42 g) in dry benzene or ether (10 ml) was added dropwise to a stirred solution of N-phenyl benzohydroxamic acid (**1a**, 10 mmol, 2.13 g) in dry benzene or ether (100 ml) at 0-5°C during 20 min. The reaction mixture was stirred at the same temperature for 30 min. and at room temperature (25°C) for 1 hr. Water (50 ml) was added. The solvent layer was washed with aqueous 5% solution of sodium hydroxide (10 ml) and then with water till free of alkali. After drying over anhydrous sodium sulphate and concentration, 2-chlorobenzanilide (**2a**, 1.90 g, 84%) was isolated, which could be recrystallised from aqueous 30% ethanol, m.p. 104°C. This versatile method can be best adopted for the preparation of 2-chloroanilines with suitable substituents (**2a** - **2i**) as indicated in Table 1.

Table 1
Conversion of hydroxamic acid derivatives into ortho-chloroarylamine derivatives.

Hydroxamic acid	Product	Yield %	Melting point °C observed	
			observed	Lit.
N-phenyl benzo-, **1a**	N-benzoyl-2-chloroaniline, **2a**	84	104	105[10]
N-(o-chlorophenyl)-benzo-, **1b**	N-benzoyl-2,6-dichloroaniline, **2b**	77	161	159[10]
N-(o-tolyl)-benzo-, **1c**	N-benzoyl-2-chloro-6-methyl-aniline, **2c**	71	146	147.5[10]
N-(o-anisyl)-benzo-, **1d**	N-benzoyl-2-chloro-6-methoxy-aniline, **2d**	85	136	135[11]
N-phenyl-salicylo-, **1e**	N-salicylo-2-chloroaniline, **2e**	85	166	166.7[12]
N-phenylaceto-, **1f**	N-aceto-2-chloroaniline, **2f**	82	86	88[13]
N-(o-chlorophenyl)-aceto-, **1g**	N-aceto-2,6-dichloroaniline, **2g**	78	173	175[14]
N-(o-tolyl)-benzo- **1h**	N-aceto-2-chloro-6-methyl-aniline, **2h**	74	162	163[15]
N-(o-anisyl)-benzo-, **1i**	N-aceto-2-chloro-6-methoxy-aniline, **2i**	84	123	123[11]

When N-phenylhydroxylamine itself was reacted with thionyl chloride under similar conditions, the product mixture contained only traces of ortho-chloroaniline and aniline as detected by GLC analysis.

The reaction apparently involves the initial formation of the chlorosulphite **3**, which subsequently undergoes a SNi' type reaction to give **4**. Finally the proton shift gives the 2-chloroanilide **2**. If the reaction is terminated prematurely by the addition of water, the chlorosulphite **3** gets hydrolysed to give the anilide **5**.



a . X=H , R=Ph
b . X=Cl , R=Ph
c . X=Cl , R=Ph
d . X=OMe , R=Ph
e . X=H , R=$\underline{o}$-HOC_6H_4
f . X=H , R=Me
g . X=Cl , R=Me
h . X=Me , R=Me
i . X=OMe , R=Me

Our reaction is entirely different from the Orton rearrangement,[6] which involves heterolysis of N-Cl bond and electrophilic substitution by chlorine. Reaction of N-phenylhydroxylamine with hydrochloric acid yields essentially the para rearrangement product.[7] However, O-acylated N-phenyl benzohydroxamic acid on heating rearranges to ortho-acyloxy benzanilide.[8] Similarly treatment of N-phenyl benzohydroxamic acid with para-nitrobenzene-sulphonyl chloride yielded ortho-(p-nitrobenzenesulphonoxy)benzanilide.[9] The last two reactions apparently involve intramolecular rearrangement similar to the reaction reported here.

Conclusion: It is thus possible to prepare orthochloroaniline and its substituted derivatives (without any contamination of para isomers) from the corresponding nitrobenzene derivatives, by initial reduction to phenylhydroxylamines, benzyoylation or acetylation, subsequent reaction with thionyl chloride and final debenzoylation or deacetylation.

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