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CARCINOGENIC REACTIONS. ARYLAMINATION WITH ARYLHYDROXYLAMINES

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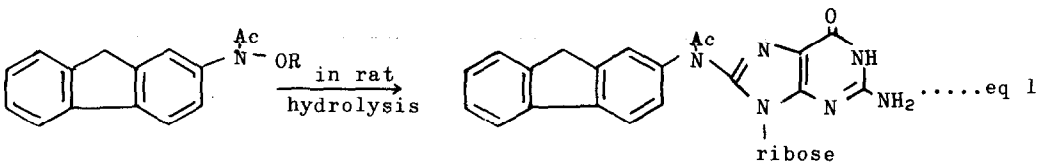
Arylhydroxylamines such as diphenyl-, 2-fluorenyl- and 2-naphthylhydroxylamines, and 4-hydroxylaminoquinoline N-oxide, and their acyl or alkyl derivatives have been implicated as agents in the carcinogenicity of corresponding aromatic nitro and amino compounds.[1] The adverse reactions have been speculated to be the consequence of covalent binding of arylhydroxylamines to cellular nucleophiles. Thus, understanding of the basic reaction of arylhydroxylamines with nucleophiles acquires considerable significance. Administration of N-acetyl-2-fluorenylhydroxylamine to rats was shown to result in the incorporation into hepatic DNA and RNA. 8-(N-2-acetoamidofluorenyl)guanosine was

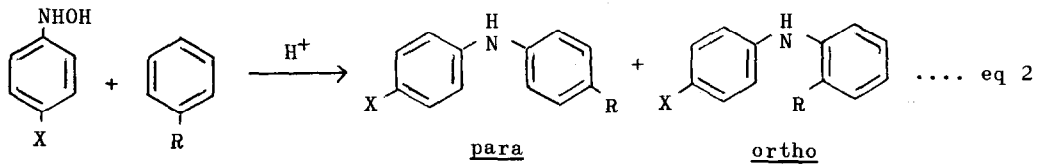


.....eq 1

identified from the hydrolysis products of the combined nucleic acid(eq 1.) Chemically, arylhydroxylamines rearrange to para-hydroxyanilines by acid catalysis(Bamberger rearrangement.)[2] Since the rearrangement is intermolecular, a variety of nucleophiles such as OH^-, CH_3O^-, and Cl^- can attack the para (or ortho)-position of the amino group.[2] The mechanisms of the reaction have been discussed and a possibility of an involvement of anilenium ions has been proposed.[3] In addition, the recent survey of the chemistry of nitrenium ions

has amply illustrated the diversity of application in organic reactions.[4)]

In view of these situations, we have discovered a reaction which involves, at least formally, the process which is closely relating to eq 1. When trifluoroacetic acid, which has low nucleophilicity, was used as the acid catalyst, arylhydroxylamines including a strong carcinogenic one, did react with aromatic compounds and give diphenylamines(eq 2.) para-Tolylhydroxylamine in 50% trifluoracetic acid - anisole below ambident temperatures in nitrogen



.... eq 2

atmosphere gave 4-methyl-4'-methoxydiphenylamine in 65.8% yield, accompanied with 4,4'-dimethoxyazoxybenzene (10.4%.) Any isomeric diphenylamine could not be identified (less than few percents if any.) Table reveals the dependence of the yields on acid concentration. The lower acid concentration increases the yield of the azoxybenzene.

Table. Yields of Diphenylamines

phenylhydroxylamine, para-X	aromatic nucleophile	CF_3CO_2H conc. in %	diphenylamine, % para	ortho
CH_3	anisole	1	5.8	
CH_3	anisole	10	11.7	
CH_3	anisole	50	65.8	(< 3)
H	benzene	50	65.5	
H	toluene	50*	55.7	21.1
H	anisole	10	1.5	0.7
H	anisole	50	8 - 21	1 - 10
H	anisole	50*	25.6	14.3
Cl	anisole	15	8.2	
phenyl	anisole	50	16.4	
OCH_3	anisole	50*	19.3	

* in the presence of ascorbic acid.

Phenylhydroxylamine and anisole in the presence of the same acid gave 4-methoxydiphenylamine and 2-methoxydiphenylamine. The dependence of the yields on the acid concentration is similar to the case of tolylhydroxylamine. The presence of a catalytic amount of ascorbic acid in the reaction mixture seems to give a better or more reproducible result (Table.) The effect could be explained by the elimination of concurrent adverse radicalic reaction. Phenylhydroxylamine can react with toluene to result in the formation of 4- and 2-methyldiphenylamines in the yields of 55.7 and 21.1%, respectively. Reaction with benzene, the simplest reaction, gave diphenylamine in 65.5%.

4-Chlorophenylhydroxylamine and anisole gave 4-chloro-4'-methoxydiphenylamine. The reaction of a strong carcinogen, 4-hydroxyaminobiphenyl with anisole yielded 4-p-methoxyanilinobiphenyl in 16.4% yield. The presence of ascorbic acid is important in the reaction of 4-methoxyphenylhydroxylamine with anisole. In the absence of ascorbic acid, the isolated product was only a strongly colored crystalline compound as the result of an instantaneous reaction at -10 - 0°. The presence of a catalytic amount of ascorbic acid much improved the reaction and 4,4'-dimethoxydiphenylamine was isolated in 19% yield.

These observations show that 1) the nitrogen atom of arylhydroxylamines can be the reaction center, 2)the attacking species formed from arylhydroxylamines is ortho-para directing, or electrophilic, 3) the reaction is acid catalysed, 4) the reaction may have a synthetic utility in place of Ullman condensation.[5] On the mechanism of the reaction, the participation of singlet or triplet nitrenium ions[6] is attracting. We are studying on the mechanism of the reaction and on the nature of other carcinogenic hydroxylamines.[7]

References

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