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Regioselective Bromination of Anilines in the Presence of Nitrosonium Hydrogensulfate in Concentrated Sulfuric Acid

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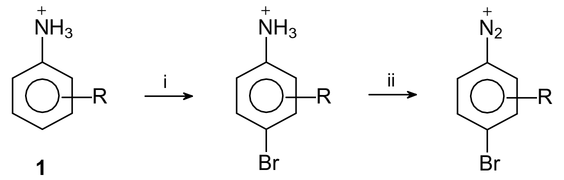
Reaction of aniline, *o*- and *m*-substituted anilines or *N,N*-dialkylanilines with bromine and nitrosonium hydrogensulfate in concentrated sulfuric acid leads to the corresponding 4-bromoanilines but no bromination takes place in the absence of nitrosonium salt.

It was shown in the previous communication[1] that aniline is not diazotised but is instead nitrated mostly at the *para*-position under action of nitrosonium hydrogensulfate and nitric acid in concentrated sulfuric acid. This allows us to consider the interaction with nitrosonium salt as a route by which to enhance the reactivity of anilinium ions towards ring substitution in highly acidic media. Based on this approach the bromination reaction is studied in the present work.

It was established that aniline in 92–100% sulfuric acid, existing in the protonated form of anilinium ion **1a**, is readily transformed to 4-bromoanilinium ion **2a** under action of bromine and nitrosonium hydrogensulfate. However, it does not react with bromine in the absence of nitrosonium salt. The reaction proceeds at room temperature or under slight heating and yields *ca.* 95% of 4-bromo derivative **2a** with an impurity of 2,4-dibromo derivative.



1 **2** **3**

a R = H
b R = 3-Me
c R = 3-Cl
d R = 2-Cl
e R = Br

Scheme 1 *Reagents and conditions:* i, H_2SO_4, $NO^+SO_4^-$, Br_2, 20–35 °C (0.01 mol of each reagent, 10 ml H_2SO_4); ii, H_2O.

According to ^{1}H and ^{13}C NMR data[†] 4-bromoanilinium ion **2a** as well as starting anilinium ion **1a**[1] is not diazotised with nitrosonium hydrogensulfate in concentrated sulfuric acid; it gives 4-bromodiazonium ion **3a** only at lower acidity. 1-(4-Bromophenylazo)-2-naphthol was obtained after dilution of the reaction mixture with water and coupling with 2-naphthol in 84% yield. Bromination with a catalytic quantity of nitrosonium salt is also possible. In the presence of 0.2 equiv. of nitrosonium hydrogensulfate anilinium ion **1a** is converted to 4-bromoanilinium ion **2a** by *ca.* 70%. The brominating power of the system is increased on increasing the sulfuric acid concentration up to 100%.

Anilines containing an alkyl group or a halogen atom in the *meta*- or *ortho*-position of the aromatic nucleus, and also *N,N*-dialkylanilines, may be brominated in the same manner. Solutions of 4-bromo-3-methyl-, 4-bromo-2-chloro-, 4-bromo-3-chloro- and 2,4-dibromobenzenediazonium salts **3b–e** were prepared by action of bromine and nitrosonium hydrogensulfate on 3-methyl-, 2-chloro-, 3-chloro- and 2,4-dibromoanilines **1b-e**, respectively, followed by dilution with water. To confirm the position of the bromine atom, the diazonium salt was in every case converted by coupling with 2-naphthol to an azo compound identical with the sample obtained from the corresponding bromoaniline synthesized by an independent route.

Brominated amines in the form of free base were isolated when diazotisation was prevented by pouring into alkali solution with addition of substances which decompose nitrous acid.

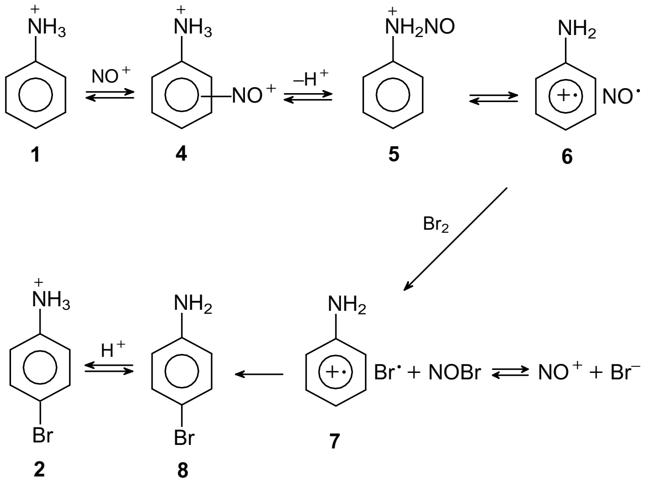
When the *para*-position is already substituted, bromination hardly proceeds. Only a small part of the 4-bromoaniline is converted to 2,4-dibromo and 2,4,6-tribromo derivatives, even under prolonged heating with a two-fold excess of bromine and nitrosonium hydrogensulfate.

The *o*-nitro group in the aromatic ring retards the reaction and decreases its selectivity while the *m*-nitro group protects it from bromination. 2-Nitroaniline remains mostly unchanged on reaction in 92% sulfuric acid but in 100% sulfuric acid at 40 °C it yields 4-bromo-2-nitro- and 4,6-dibromo-2-nitroanilines in comparable quantities.

Reaction between anilinium ions and bromine in the presence of nitrosonium hydrogensulfate in concentrated sulfuric acid followed by dilution with water is a simple method for the preparation of *p*-bromobenzenediazonium salts directly from unbrominated primary amines. The alternative methods include separate stages involving bromination of amine or its *N*-acyl derivative with subsequent hydrolysis, isolation of the product and then diazotisation.

The mechanism of the bromination reaction studied is probably similar to the mechanism of *N,N*-dimethylanilinium[2] or anilinium[1] ion nitration in sulfuric acid in the presence of nitrosonium hydrogensulfate. The intermediate formed by interaction of aromatic substrate with nitrosonium cation is attacked by reagent species. The ability of aromatic compounds to yield charge transfer π-complexes with nitrosonium ion is known[3] and is considered as an initial step in the diazotisation reacton.[4] It should be possible to observe the formation of these complexes by monitoring the appearance of the charge-transfer band in electronic spectra (for 4-bromoanilinium complex $\lambda_{\max} = 560$ nm). Deprotonation and migration of nitrosonium cation lead from π-complex **4** to *N*-nitrosoammonium ion **5**. The latter irreversibly turns into diazonium ion in less acidic media,[4] but it is stable in concentrated sulfuric acid due to hindrance of proton loss.

The key step is the transformation of *N*-nitrosoammonium ion **5** into ion-radical pair **6**. Interaction of the latter with a bromine molecule causes replacement of NO by a bromine atom, followed by recombination of radicals in ion-radical pair **7**. A new covalent bond is formed with the carbon atom with the highest spin density in the ring (4 > 2 > 3 for *N,N*-dimethylaniline cation-radical[5]). The other bromine atom adds a nitrogen oxide molecule displaced from complex **5** to give nitrosyl bromide, which dissociates to bromide anion and nitrosonium cation, thus regenerated.



Scheme 2

The influence of the nature of the *N*-alkyl group on the rate of bromination of *N,N*-dialkylaniline shows that alkyl groups are close to the reaction centre and hence ion-radical pair **6** is formed from *N*-nitrosoammonium ion **5** but not directly from π-complex **4**. When *N,N*-dimethylaniline completely converts to 4-bromo-*N,N*-dimethylaniline, *N,N*-diethylaniline reacts by only 20%.

In contrast to the nitration of anilinium ion that occurs in both the catalysed and uncatalysed path, bromination proceeds only in the nitrosonium ion catalysed mechanism. This represents an example of a new, regioselective reaction of aromatic substitution at the position *para* to the ammonium group (which is usually a typical *meta*-orientating group).

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[†] *Selected spectroscopic data.* ^{13}C NMR (90 MHz, 100% H_2SO_4) δ_{TMS}: *p*-$BrC_6H_4NH_3^+$ 124.61 (C-2, C-6), 126.91 (C-1), 127.74 (C-4), 133.82 (C-3, C-5); *p*-$BrC_6H_4NHMe_2^+$ 119.75 (C-2, C-6), 131.16 (C-3,C-5), 131.31 (C-4), 141.42 (C-1); for $PhNH_3^+$ *cf.* ref. 1.