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# DIRECT CONVERSION OF ANILINES INTO AMINOPHENOLS

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*Summary : Hydroxylation of anilines by hydrogen peroxide in $SbF_5$-HF yields the three possible aminophenols, the meta isomer being the major product. The reaction implies attack of protonated hydrogen peroxide $H_3O_2^+$ on the N-protonated substrate.*

The oxidation of aromatic amines is often complicated by several reaction paths, the structure of the products depending as much on the reagent as on the structure of the substrate[1,2].

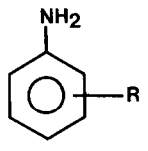
We now wish to report a new, efficient synthesis of aminophenols from anilines using hydrogen peroxide in superacidic media.

In a typical experiment 70% hydrogen peroxide (6 mmoles) was added to a cold (-20°C) stirred solution of the substrate (4 mmoles) in $SbF_5$-HF (molar ratio: 0.04; 20 ml). After 15 minutes, the solution is slowly poured over ice-water-$NaHCO_3$-ether. Products are isolated after usual work-up and chromatography over $SiO_2$.

The results summarized in table 1 deserve several comments :

- No oxidation or degradation of the nitrogen substituent is observed.

- Ring hydroxylation affords the three aminophenols, the meta isomer being the major product.

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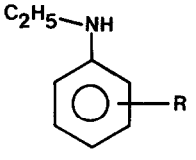


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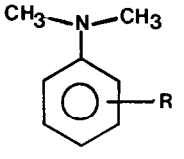


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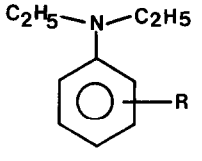


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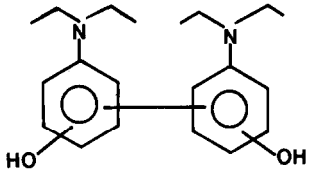
a : R = H
b : R = 2 OH
c : R = 3 OH
d : R = 4 OH

| Starting material | Molar ratio $SbF_5$-HF | Products (% yield) | Ratio ortho | meta | para |
|---|---|---|---|---|---|
| 1a | 0.04 | 1a(5) + 1b(20.5) + 1c(36) + 1d(14) | 29 | 51 | 20 |
| 2a | 0.04 | 2a(4.5) + 2b(18) + 2c(40.5) + 2d (16.5) | 24 | 54 | 22 |
| 3a | 0.04 | 3a(12) + 3b(14) + 3c(44) + 3d(26) | 17 | 52 | 31 |
| 3a | 0.03 | 3a(26) + 3b(7) + 3c(40) + 3d(15) | 11 | 65 | 24 |
| 4a | 0.04 | 4a(12.5) + 4b(11) + 4c(49) + 4d (16) | 14 | 64 | 22 |

TABLE 1

- Reactions are performed at -20°C and yields are for isolated products after purification by column chromatography over $SiO_2$.
- Phenol 4d was coeluted with a compound whose yield (6 %) was determined by NMR. Its molecular ion (m/e 328) implies an oxidative dimerisation. Its structure might be such as

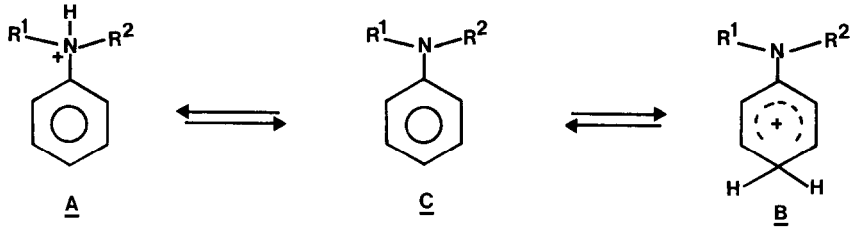



The aminophenols are stable in the reaction conditions, ruling out an initial hydroxylation on the ring followed by an isomerisation.

Furthermore an initial oxidation on the nitrogen atom can also be brushed aside : in $SbF_5$-HF, in the presence or not of hydrogen peroxide, phenylhydroxyl amine[3], nitrosobenzene, nitrobenzene or N,N dimethylaniline oxide[4] yield complex mixtures, without formation of the corresponding aminophenols.

Consequently, only a direct hydroxylation accounts for the formation of the products.

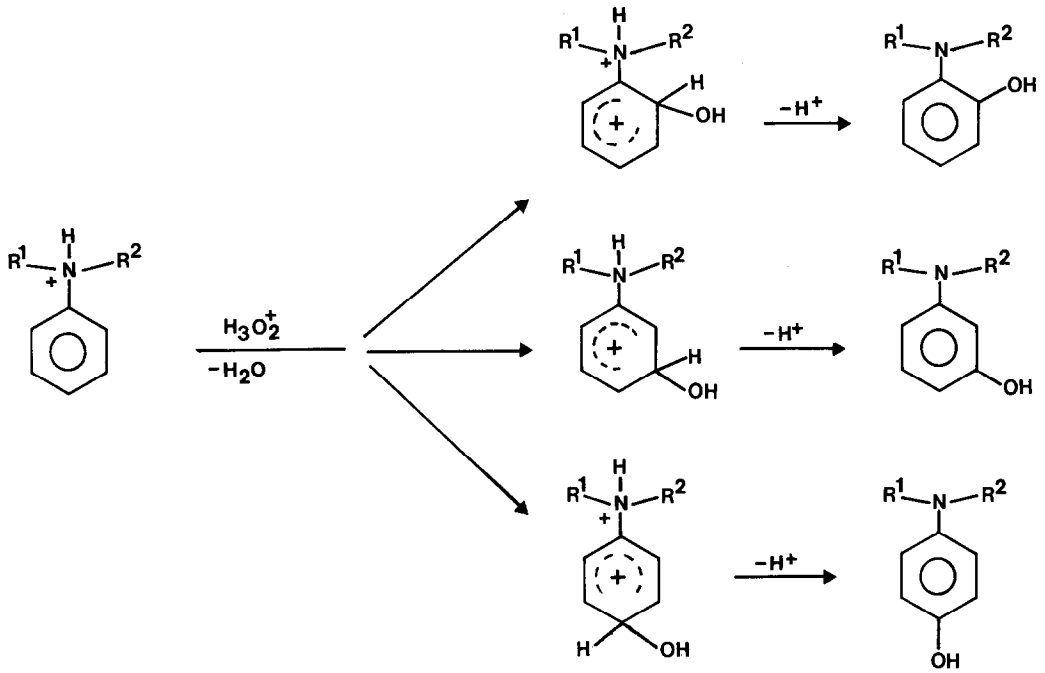
In the superacidic medium ($-21 < H_o < -19$)[5] anilines are protonated either on the ring or on the nitrogen atom[6-8], the concentration of the neutral substrate being very small.




A C B

Ion B is unreactive towards electrophiles; therefore hydroxylation by protonated hydrogen peroxide $H_3O_2^+$ [9] has to occur either on the neutral substrate C or on the nitrogen-protonated form (ion A).

Electrophilic substitution (nitration, sulfonation, bromination)[10,11] of aromatic amines in concentrated or pure sulfuric acid ($H_o$ = - 12) is known to occur overwhelmingly through the ammonium ions. It is *a fortiori* the same species (ion A) which is hydroxylated in superacid ($H_o \simeq -20$) to give the three aminophenols.




Evidence that contribution of the free amine (reaction of which would yield the ortho and para isomers) is pratically absent is supported by the results obtained with amine 3a in experiments carried out at two acidity levels (see Table). Reaction rate decreases in less acidic conditions whereas selectivity is improved to the detriment of compounds 3b and 3d. In very acidic conditions the more reactive electrophile is less selective.

The observed regioselectivity shows very similar reactivities at the meta and para positions, a phenomenon already observed in the nitration of anilines[10]. Hydroxylation at the ortho position shows a gradual decrease as the size of the nitrogen group increases.

Most oxidants react on the nitrogen substituent[1,2] and this new reaction appears to be very attractive to prepare directly aminophenols from the corresponding aromatic amines.

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