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ORGANIC SYNTHESIS
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Oxidation of 4-Aminotoluene with Ozone in Acetic Acid Solution

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Abstract—The possibility of preparing 4-aminobenzoic acid by oxidation of 4-aminotoluene with ozone in acetic acid in the presence of cobalt(II) acetate and potassium bromide was examined. The optimal oxidation conditions were found.

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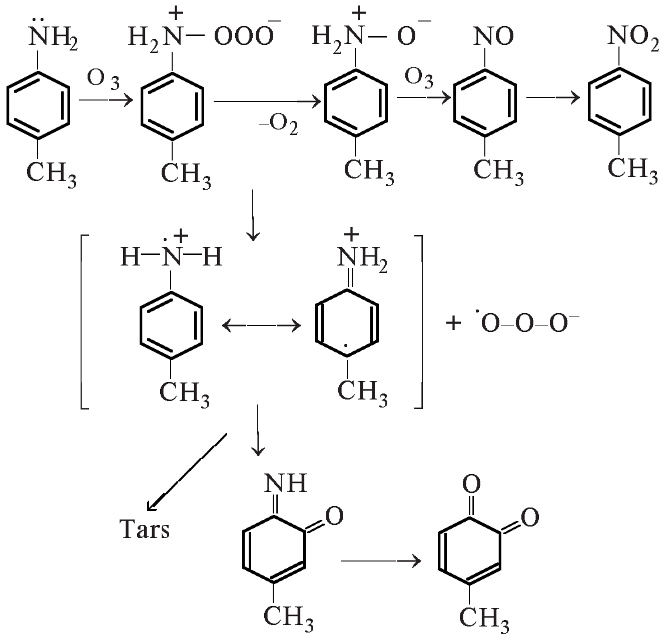
4-Aminobenzoic acid (4-ABA) is widely used in pharmaceutical industry, in particular, as an intermediate in production of anesthetics [1]. It is prepared by oxidation of 4-acetylaminotoluene (4-AAT) either with potassium permanganate or with atmospheric oxygen, followed by hydrolysis of the resulting 4-acetylaminobenzoic acid (4-AABAc) [1, 2]. The drawback of the first procedure is formation of large amounts of toxic, difficultly utilizable substances, and that of the second procedure is cumbersome implementation. A good choice may be the use of ozone, an environmentally friendly oxidant reacting under mild conditions with virtually all classes of organic compounds [3, 4].

The known method for oxidation of methylbenzenes with ozone in acetic acid [5] is unsuitable for preparing benzoic acids from methylbenzenes containing in the aromatic ring substituents with one or more lone electron pairs (–OH, $-NH_2$, etc.). It is known that methylanilines are oxidized with ozone at a high rate at the lone electron pair of the nitrogen atom with the formation of the molecular adduct $Ar\overset{+}{N}H_2-O_3^-$. Products of methyl group oxidation are not formed under these conditions [4, 6].

To examine the possibility of oxidative synthesis of aminobenzoic acids from methylanilines and develop low-waste processes, we studied the liquid-phase reaction of ozone with 4-aminotoluene (4-AT) in an acetic acid solution.

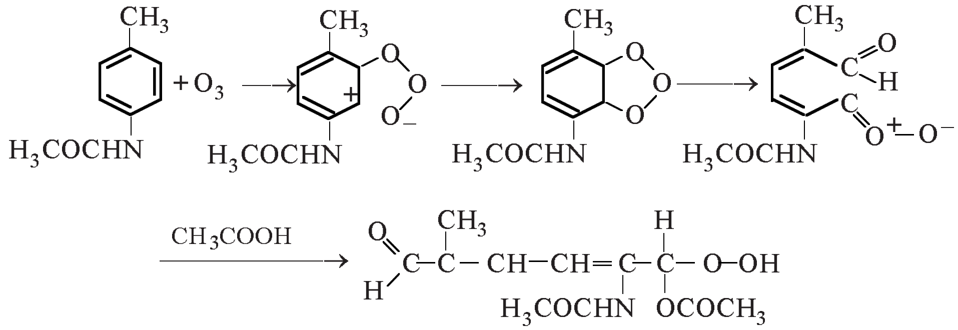
Preliminary studies [6] showed that ozone in an acetic acid solution reacts with 4-AT at a high rate ($k_{app} = 2.5 \times 10^3$ l mol^{-1} s^{-1}, 20°C). The major reaction products are tars. Also, 4-nitrosotoluene, 4-nitrotoluene, and traces of toluquinone are formed. The product composition is essentially similar to that described in the literature [4, 6] and corresponds to the scheme suggested for the reaction of ozone with aromatic amines [6]:



The scheme suggests fast attack of ozone at the lone electron pair of the nitrogen atom with the formation of an ion–radical pair which, depending on the structure of the amine, transforms into various products, the majority of which are unidentified polymeric tars. The absence of products of methyl group oxidation is due to the fact that the reactivity of 4-AT along this pathway is almost three orders of magnitude lower than that of the amino group [8].

To prevent the reaction of the amino group with ozone, we protected it by acylation. 4-Acetylaminotoluene was dissolved in glacial acetic acid, and an ozone–air mixture with an ozone concentration of 4.5×10^{-4} M was passed through the solution. Kinetic studies showed that the reactivity of acylated 4-AT toward ozone decreases considerably. The rate constant of the reaction is $k_{app} = 28.7$ l mol^{-1} s^{-1} at 20°C. Drastic decrease in the rate constant of the reaction of ozone with 4-AAT suggests a change in the reaction mechanism.

Apparently, ozone under these conditions attacks not the NH group but mainly double bonds of the aromatic ring (85%) and, to a lesser extent, the methyl group (15%) (see figure). In accordance with the results of the study, 1.36 mol of ozone is consumed at 20°C per mole of 4-AAT. At such ozone consumption, the reaction with the aromatic ring, presumably, follows the scheme [9]



Among the methyl group oxidation products, 4-acetylaminobenzaldehyde (4-AABAl) prevails in the early reaction steps, and 4-AABAc, in the late steps (see figure).

The rate and selectivity of 4-AAT oxidation at the methyl group increase with temperature and on adding a catalyst, cobalt(II) acetate. The reaction becomes fast, and its major product is 4-AABAc. At 4-AAT concentration of 0.4 M, cobalt(II) acetate concentration of 0.14 M, and temperature of 95°C, the oxidation is complete in 40 min, and the selectivity with respect to the methyl group is 52%.

Addition of KBr increases the rate and selectivity of oxidation at the methyl group. The 4-AABAc yield reaches 75%. Among methyl group oxidation products, we also detected 4-acetylaminobenzyl bromide (4-AABB) and traces of 4-AABAl.

Selective oxidation at the methyl group in the presence of cobalt(II) acetate and potassium bromide becomes possible owing to two-step oxidation with ozone. Ozone predominantly reacts with Co^{2+} ($k_1 = 9.3 \times 10^2$, $k_{(AcNHArCH_3 + O_3)} = 28.7$ l mol^{-1} s^{-1}, our data) with the formation of Co^{3+} active species [reaction (1)]. The subsequent reaction (2) yields the complex $Co^{2+}Br^{\bullet}$ [10], which involves 4-AAT into fast and selective oxidation at the methyl group [reaction (5)]:

$$Co^{2+} + O_3 + H^+ \rightarrow Co^{3+} + HO^{\bullet} + O_2, \qquad (1)$$

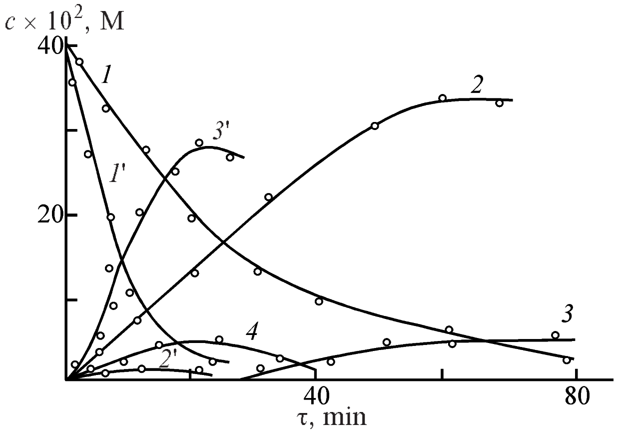
$$Co^{3+} + Br^- \rightarrow Co^{3+}Br^- \rightleftarrows Co^{2+}Br^{\bullet}, \qquad (2)$$

$$Br^- + O_3 + H^+ \rightarrow Br^{\bullet} + HO_3^{\bullet}, \qquad (3)$$

$$AcNHArCH_2^{\bullet} + Br^{\bullet} \rightarrow AcNHArCH_2Br, \qquad (4)$$

$$AcNHArCH_3 + Co^{2+}Br^{\bullet} \rightarrow AcNHArCH_2^{\bullet} + Co^{2+} + Br^- + H^+. \qquad (5)$$

To provide the occurrence of reaction (1), ozone should be continuously fed to the reaction system.



Variation of the concentrations *c* of components of the reaction mixture in oxidation of 4-AAT with ozone–air mixture at (*1*–*4*) 20 and (*1*'–*3*') 95°C in the presence of cobalt(II) acetate and potassium bromide. $[4\text{-AAT}]_0 = 0.4$, $[O_3]_0 = 4.5 \times 10^{-4}$, $[Co(OAc)_2]_0 = 0.1$, $[KBr]_0 = 0.1$ M, $v_{air} = 8.3 \times 10^{-3}$ l s^{-1}. (τ) Time. (*1*, *1*') 4-AAT, (*2*) peroxides, (*2*') 4-AABB, (*3*, *3*') 4-AABAc, and (*4*) 4-AABAl.

Interruption of the ozone supply leads to deceleration and complete termination of the process. This fact additionally confirms the formation of active catalyst species mainly by reactions (1) and (2). Under the experimental conditions, the concentration of molecular oxygen in the gas mixture is 15 times higher than that of ozone. Therefore, the acetylaminobenzyl radical formed in the system reacts predominantly with the oxygen molecule [reaction (6)] to form acetylamino peroxy radical which subsequently yields the final products [reaction (7)]:

$$\mathrm{AcNHArCH_2^{\bullet} + O_2 \rightarrow AcNHArCH_2O_2^{\bullet}}, \qquad (6)$$

$$\mathrm{AcNHArCH_2O_2^{\bullet} \rightarrow products.} \qquad (7)$$

4-AABB can appear in the system owing to the occurrence of reactions (3) and (4).

An increase in the rate and selectivity of 4-AAT oxidation in the presence of KBr is due to accumulation of the active complex $\mathrm{Co^{2+}Br^{\bullet}}$, which involves the substrate in oxidation at a higher rate than does the oxidized form of cobalt [10].

EXPERIMENTAL

In the experiments we used analytically pure grade glacial acetic acid purified by vacuum distillation from potassium permanganate. Crystalline 4-AT was purified by repeated recrystallization from water. Cobalt(II) acetate and potassium bromide (analytically pure grade) were used without additional purification.

The calculated amount of 4-AT was dissolved in acetic anhydride in a flask at 20°C. The mixture was stirred for 15 min. After the acylation completion, the mixture was poured into ice-cold water. The 4-AAT precipitate was separated, washed with a 5% NaOH solution and water, and dried in a vacuum desiccator. Yield 94%.

A glass column equipped with a porous partition for dispersing an ozone–air mixture was loaded with 10 ml of acetic acid, 0.4 M of 4-AAT, and calculated amount of the catalyst, after which the unit was thermostated and, after attainment of the steady-state mode of ozonizer operation, an ozone–air mixture containing 4.5×10^{-4} M ozone was passed at a rate of 30 l $\mathrm{h^{-1}}$. After the oxidation completion, the mixture was poured into a glass beaker filled to 2/3 with finely crushed ice, after which the mixture was diluted with cold water to a total volume of 50 ml. The precipitated 4-AABAc was filtered off, washed with cold water, and dried. Then 10 ml of concentrated HCl, 20 ml of water, and 4 ml of alcohol were added, and the mixture was refluxed for 1 h with stirring. After cooling, the precipitated 4-ABA was filtered off. Yield 68% based on the loaded 4-AAT.

The ozone concentration in the gas phase was determined spectrophotometrically from the absorption at 254–290 nm. The oxidation products were identified and quantitatively determined in solution by GLC on a chromatograph equipped with a flame ionization detector. The column, 2 m long and 4 mm in diameter, was packed with Chromaton N-AW impregnated with SE-30. Chromatographing conditions: vaporizer temperature 250°C, column temperature 180°C; flow rates, l $\mathrm{h^{-1}}$: carrier gas (nitrogen) 1.8, hydrogen 1.8, and air 18. 4-Nitrochlorobenzene was used as internal reference.

The running concentration of 4-AABAc was determined by alkali titration. A 0.5-ml sample was taken from the reaction mixture, the solvent was distilled off, and the dry residue was dissolved in 30 ml of 50% ethanol. The solution was titrated with 0.05 N NaOH using phenolphthalein as indicator.

CONCLUSIONS

(1) Ozone reacts with 4-aminotoluene in acetic acid at a high rate, mainly at the nitrogen atom. Products of methyl group oxidation are not formed under these conditions. The direction of the ozone attack can be changed to the methyl group and benzene ring by amino group acylation; however, under these conditions, the yield of aromatic products does not exceed 15%.

(2) The selectivity of oxidation of 4-acetylaminotoluene increases to 52% with increasing temperature to 95°C and on adding a catalyst, cobalt(II) acetate. Addition of potassium bromide leads to a further increase in the rate and selectivity of the methyl group oxidation. The yield of 4-acetylaminobenzoic acid reaches 75%.

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