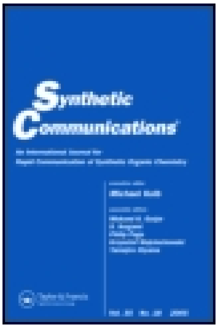

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A New Approach to the Oxidation of Methylquinolines with Selenium Dioxide

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A NEW APPROACH TO THE OXIDATION OF METHYLQUINOLINES WITH SELENIUM DIOXIDE

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ABSTRACT: A study of some parameters which influence the oxidation of 2- and 4-methylquinolines with selenium dioxide (or selenious acid) in dioxane has allowed to correct some erroneous opinions of this method and to elaborate a general, simple, fast, and cheap procedure of oxidation of methylquinolines having a methyl group in the position 2 or 4.

Quinoline aldehydes are important synthetic intermediates in the synthesis of heterocyclic compounds. Oxidation of methylquinolines with selenium dioxide is the simplest method for the preparation of quinoline aldehydes but the conviction that high yields of the aldehydes can be reached only when freshly sublimed SeO_2 is used for the reaction, has been common and became consolidated in monographs[1]. The necessity of purification of highly toxic SeO_2 by sublimation at 340°C is a cosiderable limitation of applicability of this simple oxidant.

We investigated the influence of the molar ratio SeO_2 (or selenious acid) to 2-methylquinoline (quinaldine) or 4-methylquinoline (lepidine), reaction time, temperature and content of water in selenium dioxide on yield of oxidation products. These aldehydes were isolated as 2,4-dinitrophenylhydrazones and quinaldic acid (2-quinolinecarboxylic acid) as the copper(II) salt.

The best yields of aldehydes are reached if the excess of the oxidant was used. Its kind (SeO_2 or H_2SeO_3) and purity do not effect the reaction course. In boiling dioxane yields were 50-56% for 2-quinolinecarboxaldehyde and 75-85% for 4-quinolonecarboxaldehyd. In these conditions oxidation of quinoline aldehydes to carboxylic acids runs very slowly (about 50h) so do not influence on the yield of aldehydes. Oxidation of quinaldine at room temperature gives better yield of aldehyde (70%) but the process has to last for two weeks.

The insufficiency of the oxidant (for example SeO_2 stored over the prolonged period of time which results in diminished content of SeO_2) causes sharp drop of yield of aldehyde observed by Kaplan[2] and increase of amount of side-products.

In the case of quinaldine, when the excess of oxidant is used, isolation of valuable quinaldic acid is more difficult because it forms a stable compound with the excess of selenious acid whereas 4-quinaldinecarboxylic acid does not form analogical compound. This compound can be decomposed only by the reduction of H_2SeO_3 to selenium (e.g. with SO_2) or by treating with solution of cupric sulfate which precipitate cupric salt of quinaldic acid. After removal of H_2SeO_3 quinaldic acid can be isolated from aqueous solution at the isoelectric point (pH 3.2).

The formed quinolinecarboxylic acid catalyses secondary reactions of the aldehyde both during oxidation and purification of products. These reactions are strongly promoted when unreacted quinaldine is present in the medium.

Thus we investigated the influence of the content of quinolinecarboxylic acid on efficiency of steam-distillation of products and formation of tarry products. We have found that the presence of quinaldic acid causes sharp drop yield of aldehyde. For example, the mixture of pure 2-quinolinecarboxaldehyde, quinaldine and quinaldic acid in molar ratio 9:1:0.8, after steam-distillation, gave 75% of tarry products.

Summing up, we have showed that the successful result of oxidation of methylquinolines to aldehyds with selenious acid is depended on amount of the oxidant used and on <u>neutralization</u> of quinolinecarboxylic acid in the reaction products before isolation of aldehyde.

The results obtained during oxidation of quinaldine and lepidine were basis for elaboration of the general method of oxidation of methylquinolines, having a methyl group in position 2 or 4, on a preparative scale.

To prove the universality of this method seven various methylquinolines were oxidized to aldehydes in good yields namely: quinaldine 55%, lepidine 78%, 2,6-dimethylquinoline 79%, 8-acetoxyquinoline 51%, 4-methoxy-2-methyl quinoline 49%, 6-chloro-2-methyl-8-nitroquinoline 61%, 6-methoxy-2-methyl-8-nitroquinoline 72%.

The fact that the quality of the oxidant and dioxane (the mixture may contain water up to 30%) has no effect on the yield of aldehyde, makes the elaborated method simple, effective and very cheap, since it provides the possibility of use crude selenious acid obtained by simple dissolving of Se in HNO_3.

EXPERIMENTAL

General, preparative method for the oxidation of 2- and 4-methylquinolines

To a boiling solution of H_2SeO_3 (0.15 mol) in 120 ml of dioxane, containing 4-20% of water, methylqunoline (0.1 mol) in dioxane (25ml.) is added. The mixture is refluxed until all methylquinolidine is consumed (monitoring by TLC, approximately 0.25-1h). The precipitated Se is filtered off from the hot reaction mixture. Dioxane and water are distilled off under reduced pressure. The residue is alkalized with saturated aqueous $NaHCO_3$ and the mixture stirred vigorously, untill precipitated oil solidified.

After cooling, crystalline crude aldehyde is filtered off, washed with water and air-dried Crude aldehyde is purifired by steam distillation or recrystallization.

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