Prospects of Wasteless Technologies of Selective Alcohols Oxidation

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Abstract. The effect of aliphatic and heterocyclic amines on the selective oxidation reaction of alcohols by the catalytic system 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-acetylamino-TEMPO) - iodine was researched. Diethylamine, triethylamine, piperidine, 2,2,6,6-tetramethylpiperidine (pKa 11.01-11.12 ) and pyridine, 4-acetylpyridine, quinoline, isoquinoline ( pKa 4.8-5.4) were used for research. An almost waste-free method was developed for preparation esters from aliphatic alcohols by oxidizing in a two-phase medium 

CH₂Cl₂ - an aqueous solution of NaHCO₃ by a two-mediator 4-acetylamino-2,2,6,6-tetramethylpiperidin-1-oxyl - iodine catalytic system, which allows selective oxidation alcohols in one stage. The results of the study may find application in the chemical, pharmaceutical and agrochemical industry, since the developed method is environmentally and economically beneficial, and the oxidation of alcohols in order to obtain various carbonyl and carboxyl compounds in these industries is one of the priority areas.

1. Introduction

Selective oxidation of alcohols using catalytic amounts of nitroxy radicals such as TEMPO and a secondary oxidant is one of the most promising methods for producing various carbonyl and carboxyl compounds at the moment [1]. It should be noted the universality of the electrochemical methods of oxidation of benzyl, allyl and aliphatic alcohols in the presence of TEMRO, since as a result, the corresponding carbonyl compounds are obtained in good yield and selectivity [2]. Under similar conditions in an aqueous solution, polyhydric alcohols and carbohydrates smoothly turn into valuable glucononates [3]. Oxidation methods using the TEMPO system - a secondary oxidizing agent are widely used in the chemical, agrochemical, and pharmaceutical industries [4–8]. They have a number of significant advantages. For example, they can be performed in mild and economically advantageous conditions, to produce high-purity products with minimal or no waste, regardless of the substrate and the composition of the solvent mixture [5, 9-14]. Catalytic reactions using nitroxy radicals are more suitable for large-scale or industrial use [15, 16].

Oxidation of primary alcohols to the corresponding esters in one step is an important synthetic task. In recent years, the methods of organocatalytic oxidation of alcohol to esters characterized by the intermediate formation of aldehydes are gaining popularity [17].

Pyridine bases, aliphatic and heterocyclic amines are proton acceptors, and therefore should catalyze the oxidation of alcohol. The presence of such compounds in the reaction mixture changes reaction course [18].
Therefore, from a practical point of view, it was interesting to study the effect of amines on the oxidation of alcohols by a two-mediated catalytic system 4-acetylamino-TEMPO - iodine in a two-phase system (methylene chloride - an aqueous solution of sodium bicarbonate). For research amines of two groups with a pKa of 11.01-11.12 (diethylamine, triethylamine, piperidine, 2,2,6,6-tetramethylpiperidine) and with a pKa of 4.8-5.4 (pyridine, 4-acetylpiperidine, quinoline, isoquinoline) were used. The amines of the first group (pKa 11.01–11.12) are good proton acceptors. They contribute to an increase in the rate of oxidation of alcohols (optimum pH 11) [19, 20]. In addition, it is known that the oxidation reaction direction can be changed in the presence of pyridine (pKa 5.2).

Activated alcohols are converted not only to aldehydes but also to the corresponding esters in the presence of pyridine [19]. According to these data, the second group of compounds, such as pyridine and pyridine derivatives (pKa 4.8-5.4) were investigated also.

2. Method / experiment

Chemical oxidation of primary and secondary alcohols (aliphatic, aromatic, and cyclic) was carried out in CH2Cl2 - an aqueous solution of NaHCO3 in the presence of an amine and catalytic system iodine - 4-acetylamino-TEMPO. At approximately the same pKa the change in the oxidation reaction rate depended on the structure of the amine. This indicates the influence of spatial factors on the oxidation reaction.

For example, at a ratio of 4-acetylamino-TEMPO/amine - 1/0.1 diethyl- and triethylamine, the oxidation of primary alcohols is accelerated by a factor of 1.5 to 2 almost as much as piperidine and 2,2,6,6-tetramethylpiperidine (2,2,6,6-TMP). At the ratio 4-acetylamino-TEMPO/amine - 1/1, the amines of different groups act differently: diethyl and triethylamine inhibit the oxidation reaction completely, and 2,2,6,6-TMP still promotes the oxidation process but to a lesser extent. This can be explained by the different stability of ion pairs, which are formed between charged particles - participates in the oxidation reaction. At the ratio 4-acetylamino-TEMPO/amine - 1/10 the oxidation reaction of alcohols is blocked completely. It is important to note that the spatially-hindered 2,2,6,6-TMP is one of the strongest organic bases, the oxidation reaction of alcohols does not slow down. Therefore, 2,2,6,6-TMP can be used to bind a proton during the oxidation reaction in an organic solvent. In the absence of amines, alcohols are oxidized to the corresponding carbonyl compounds with a quantitative yield on the alcohol that has reacted, but the degree of alcohol conversion in this case is small (no more than 40%).

Several attempts of directly oxidize non-activated alcohols with oxoammonium salts to esters have been made. There are many examples of the oxidation of alcohols to esters using transition metals as catalysts [21]. Symmetric esters with satisfactory yield by the oxidation of TEMPO alcohols by using tetrachlororocyanuric acid as a secondary oxidant in absolutely anhydrous acetonitrile can be obtained [22]. The use of such compounds has negative environmental impact. The complexity of the implementation and use of a very aggressive primary oxidizer limits the use of this one-step method of producing symmetric esters. Oxidative esterification of aldehydes with a stoichiometric amount of an oxoammonium salt in the presence of 1,3-trifluoromethylpropanol-2 is described [20].

In our work the presence of pyridine (pKa 5.2) in catalytic amounts (alcohol / nitroxyl radical / amine - 1 / 0.1 / 0.1) allowed us to obtain carbonyl compounds and the corresponding ester. In this case the yield of the ester was 60-90% (according to GCMS, table). Other pyridine bases direct the reaction towards the formation of esters too. The yield of esters is low which is probably due to the low spatial availability of the nucleophilic center.

The results of oxidation of alcohols by the catalytic system 4-acetylamino-TEMPO - iodine in a two-phase system methylene chloride - an aqueous solution of NaHCO3 in the presence of various amines are given in table. The ratio of alcohol / nitroxyl radical / amine 1/0,1/0,1, the reaction time is 3 hours. Reaction conditions are given in the method of oxidation.
Table 1. The results of oxidation of alcohols by the catalytic system 4-acetylamino-TEMPO – iodine.

| Alcohol       | Amine          | pK$_a$  | The yield (%) |
|---------------|----------------|---------|---------------|
|               |                |         | aldehyde      | ester |
| 1-Heptanol    | Diethylamine   | 11.09   | 40            | 0     |
|               | Triethylamine  | 11.01   | 100           | 0     |
|               | Tetramethylpiperidine | 11.07 | 98            | 28.5  |
|               | Piperidine     | 11.12   | 91.5          | 90    |
|               | Pyridine       | 5.21    | 10            | 0     |
|               | 4-Acetipyridine| 4.80    | 80            | 20    |
|               | Quinoline      | 4.87    | 88            | 12    |
|               | Isoquinoline   | 5.40    | 84.5          | 15.5  |
| 1-Octanol     | Diethylamine   | 11.09   | 100           | 0     |
|               | Triethylamine  | 11.01   | 100           | 0     |
|               | Tetramethylpiperidine | 11.07 | 95            | 5     |
|               | Piperidine     | 11.12   | 76            | 24    |
|               | Pyridine       | 5.21    | 15            | 85    |
|               | 4-Acetipyridine| 4.80    | 90            | 10    |
|               | Quinoline      | 4.87    | 89            | 11    |
|               | Isoquinoline   | 5.40    | 87            | 13    |
| 1-Nonanol     | Diethylamine   | 11.09   | 100           | 0     |
|               | Triethylamine  | 11.01   | 100           | 0     |
|               | Tetramethylpiperidine | 11.07 | 97            | 3     |
|               | Piperidine     | 11.12   | 98            | 2     |
|               | Pyridine       | 5.21    | 35            | 65    |
|               | 4-Acetipyridine| 4.80    | 90            | 10    |
|               | Quinoline      | 4.87    | 92            | 8     |
|               | Isoquinoline   | 5.40    | 86            | 14    |
| Benzyl alcohol| Diethylamine   | 11.09   | 100           | 0     |
|               | Triethylamine  | 11.01   | 100           | 0     |
|               | Tetramethylpiperidine | 11.07 | 96            | 4     |
|               | Piperidine     | 11.12   | 92            | 8     |
|               | Pyridine       | 5.21    | 41.3          | 58.7  |
|               | 4-Acetipyridine| 4.80    | 95            | 5     |
|               | Quinoline      | 4.87    | 91            | 9     |
|               | Isoquinoline   | 5.40    | 96            | 4     |
| 2-Phenylethan-1| Diethylamine   | 11.09   | 100           | 0     |
| 2-Hexanol     | Diethylamine   | 11.09   | 100           | 0     |
The advantages of the proposed method of oxidation are the use of catalytic amounts of nitroxyl radical with respect to the substrate. The radical is easily regenerated and reused (number of cycles 5-6). From the point of view of ecology, nitroxyl radicals are more preferable since they are free from heavy metals, stable and non-explosive. The use of catalytic amounts of nitroxyl radicals instead of the stoichiometric amount of other reagents leads to decrease in the synthesis costs by several tens of times. Iodine is a mild reagent, does not cause halogenation and over oxidation substrate [23]. Excess iodine that has not reacted can be easily removed with thiosulfate.

In the method developed by us, pyridine is used in catalytic amounts (alcohol/amine - 1/0.1), in contrast to the known data 1/1 (2.2) [19]. From the reaction mix methylene chloride is easily separated and can be reused.

For research used reagents company "Aldrich". Gas chromatography-mass spectrometry was performed on an Agilent 7890A chromatograph equipped with an Agilent 5975C mass-selective detector (EI, 70 eV) and an HP-5MS capillary column. To identify the peaks of the chromatograms obtained, the mass spectra of the analyzed substances were compared with the mass spectra of the NIST library. Instrument control, data collection and processing was performed using the MSDChemStation software package. For the quantitative analysis, the peak areas of the analyzed substances were used, which were measured using an auto-integrator in the MSD ChemStation program.

**General method for the oxidation of alcohols by the system 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxyl – iodine**

In a 50 ml flat-bottomed flask equipped with a reflux condenser and a magnetic stirrer, 12 ml of a 0.1 M solution of sodium hydrocarbonate, 0.084 g (0.4 mmol) of 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxyl, are placed. To the resulting solution add 4 mmol of the corresponding alcohol dissolved in 12 ml of methylene chloride (the molar ratio of alcohol: nitroxyl radical is 10: 1).

With vigorous stirring with a magnetic stirrer, 2.0 g (8 mmol) of crystalline iodine is quickly added to the two-phase system. The mixture is stirred for 3 hours at room temperature (20-25°C). Then the aqueous and organic layers are separated. The aqueous layer is additionally extracted with methylene chloride (2 × 15 ml), the organic extracts are combined, treated with 20% sodium thiosulfate solution (to remove excess iodine) and the chromatographic analysis of the organic layer is carried out. These GHMS are given in the table. The reaction in the presence of amines is carried out similarly, by adding 4 mmol or 0.4 mmol of the corresponding amine to the reaction mixture (the molar ratio amine / nitroxyl radical / alcohol is correspondingly 1 / 0.1 / 0.1.

|                  | 11.01 | 11.07 | 11.09 | 11.12 | 4.80 | 4.87 | 5.40 | 92.4 |
|------------------|-------|-------|-------|-------|------|------|------|------|
| Triethylamine    |       |       |       |       |      |      |      |      |
| Tetramethylpiperidine |     |       |       |       |      |      |      |      |
| Piperidine       | 11.01 | 11.07 | 11.09 | 11.12 |      |      |      |      |
| Pyridine         | 5.21  | 100   | 100   | 100   |      |      |      |      |
| 4-Acetipyridine  | 4.80  | 100   | 100   | 100   |      |      |      |      |
| Quinoline        | 4.87  | 100   | 100   | 100   |      |      |      |      |
| Isoquinoline     | 5.40  | 100   | 100   | 100   |      |      |      |      |

* The yield of products is determined according to GHMS.
3. Conclusion
A one-pot method for the selective oxidation of alcohols in a two-phase medium (CH$_2$Cl$_2$ - an aqueous solution of NaHCO$_3$) using a two catalytic system (4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxyl - iodine) was developed. In the presence of pyridine, it allows to obtain corresponding symmetric esters with high yield and in the presence of diethyl or triethylamine only carbonyl compounds. The prospect of the work done is confirmed by the fact that, compared with the known methods the use of esters which distinguishes environmental and economic components.

4. References
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