Potassium peroxodisulfate: A convenient oxidizing agent for aromatization of 1,4-dihydropyridines

H R Memarian*, I Mohammadpoor-Baltork, M M Sadeghi & Z S Samani
Department of Chemistry, Faculty of Sciences, University of Esfahan, Esfahan 81744, Iran
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A series of 13 different 4-substituted 2,6-dimethyl-3,5-diehtoxy carbonyl)-1,4-dihydropyridines have been oxidized to pyridine derivatives by potassium peroxodisulfate in dry and wet acetonitrile solution at reflux condition. Formation of two kinds of products has been observed depending on the type of 4-substituent. Addition of water affects only the rate of oxidation.

Oxidation of 1,4-dihydropyridines, Hantzsch esters, and formation of pyridine derivatives has been of great interest for several years and are still under intensive investigation. The importance of this reaction is due to its similarity to the oxidative metabolism of these compounds in the liver to form pyridine derivatives, which become biologically inactive. Hence, a convenient method for the conversion of 1,4-dihydropyridines to pyridine derivatives is important for the identification of its metabolites.

In the course of our study on 1,4-dihydropyridines, especially photochemical oxidation of these compounds, we were interested to investigate thermal oxidation of these compounds. Although a lot of oxidants have been used for this purpose, we would like to introduce potassium peroxodisulfate as an efficient and inexpensive reagent for the oxidation of these compounds.

Peroxodisulfate ion is known as one of the strongest oxidizing agents in aqueous and protic organic solvents with redox potential about 2.01 V. The oxidative application of peroxodisulfate ion in organic synthesis has been widely investigated. Potassium peroxodisulfate has been used before for the oxidation of alkyl aryl sulfides to the corresponding sulfones.

We report herein the oxidation of 13 different 1,4-dihydropyridines 1-13 with potassium peroxodisulfate in dry and wet acetonitrile. The results are collected in Table I.

Table I shows that the expulsion of 4-substituent

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>Dry acetonitrile</th>
<th>Wet acetonitrile&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Product</th>
<th>Melting point °C</th>
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<tr>
<td></td>
<td></td>
<td>Time(min) Yield( %)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Time(min) Yield( %)&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Observed</td>
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<tr>
<td>1</td>
<td>H</td>
<td>15</td>
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<td>96</td>
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<sup>a</sup> Acetonitrile/water (20:1). <sup>b</sup> Isolated yield. <sup>c</sup> All products are known, they were identified by comparison of their physical and spectroscopic data with those of authentic samples.
and formation of unsubstituted pyridine derivatives at position 4 (compound 14) have been observed, when this group is secondary alkyl group (5) or benzyl group (4). However in the cases of methyl or aryl and heteroaryl groups (2, 3, 6-13) at this position, retention of these groups and formation of corresponding pyridine derivatives (15, 16, 17-24) have been observed. Addition of water does not change the type of product, but increases the rate of oxidation due to better solubility of oxidant in CH₃CN/H₂O. In comparison with other oxidizing agents for the oxidation of 1,4-dihydropyridines l-7, we found the potassium peroxodisulfate as a convenient oxidizing agent due to low reaction time, easy work up, and high yield of products.

Experimental Section
Starting materials 1-13 have been prepared according to the published procedures 2,11,12,25.

General procedure for the oxidation of 1,4-dihydropyridines. To a solution of 1 mmole of each of 1,4-dihydropyridines 1-13 in 2 mL acetonitrile or 2 mL acetonitrile/water (20:1) was added 1 mmole of potassium peroxodisulfate and the mixture was refluxed with stirring under protection of reaction mixture from light for the period given in Table I. After the completion of the reaction (TLC), the mixture was concentrated by evaporation of solvent, precipitated stuff was filtered and the products were purified by PLC, using carbon tetrachloride-ethyl acetate (7:1) as eluent. Solid products were recrystallized from appropriate solvents.

References