STEREOSELECTIVE 7α-HYDROXYLATION OF 3β-ACETOXY-Δ5-STEROIDS BY Fe(PE)₃/H₂O₂/MeCN

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Stereoselective 7α-hydroxylation reaction of Δ⁵-steroids by a Fe(PE); picolinate)/H₂O₂/MeCN system is presented. The 7α-hydroxylation reactions were achieved in 33-40% yields by addition of 30%-H₂O₂ to a solution of 3β-acetoxy-Δ⁵-steroids 1a-1d and a crystalline of Fe(PE)₃ in MeCN.

KEY WORDS oxygenation; 7α-hydroxylation; Fe(PE)/H₂O₂/MeCN; Δ⁵-steroid; Gif system

Stereoselective 7α-hydroxylation of 3β-acetoxy-Δ⁵-steroids is interesting in terms of the syntheses of recently discovered cytotoxic 3β,7α-dihydroxy-Δ⁵-steroids ¹ and the metabolism of cholesterol by the cytochrome P-450 species 7α-hydroxylase in the livers of most mammalians. Many investigations on oxygenation reactions using simple, readily available reagent systems mimicking mono-oxygenase enzymes have been carried out. Of those, a study on iron(II) or iron(III) picolinate (PA) complexes as a catalyst of oxygenation reactions raised challenging problems. It was also noted that the oxidation reaction with H₂O₂ catalyzed by iron picolinate complexes varied depending on the solvents used.² Although many studies on iron picolinate complex /H₂O₂/solvent systems have been reported by the Sawyer group² and Barton group,³ there has been no report to date on the oxidation reaction by the Fe⁰(PA)/H₂O₂/MeCN system. We report that the modified system Fe(PE)₃/H₂O₂/MeCN as an alternative to the Gif system reagent is effective in stereoselective 7α-hydroxylation of 3β-acetoxy-Δ⁵-steroids 1a-1d.

The oxygenation reactions with this system of 3β-acetoxy-Δ⁵-steroids, cholesterol acetate (1a), stigmasterol acetate (1b), pregnenolone acetate (1c), and dehydroandrosterone acetate (1d) were carried out according to the procedure shown in Table 1. The above reaction gave 7α-hydroxy derivatives 2 (33-40% yields) along with a trace amount of 7β-hydroxy derivatives 3, 7-oxo derivatives 4 (16-23% yields), α and β epoxides mixtures 5 and 6 (3-13% yields), and recovered materials in all cases (Chart 1). The structural identification of 2 and 3 was done by comparing the physical data of the corresponding dihydroxy compounds prepared by hydrolysis with those of the respective authentic samples,⁴α,β,c,e respectively. The structure of 4, 5, and 6 was identified by comparison of the physical data with those of the respective authentic samples.⁴b,d,e In this investigation, we found that the most efficient and stereoselective 7α-hydroxylation reaction was obtained in all cases using a molar ratio of substrate 1 : Fe(PE)₃ : 30% H₂O₂ = 1 : 0.5 : 3.

The reaction mechanism with substrates 1a-1d using the present reagent system can be postulated as shown in Chart 2, and the complexes circulate in the order of (B)→(C)→(D)→(E) or (F)→→(B). Preferential 7-hydroxylation compared to 7-ketonization may be due to the greater formation of (E) relative to (F) as a result of the sufficient H₂O contained in 30% H₂O₂.

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Table 1. Oxygenation of Δ^4-Steroids 1a-1d with Fe(III)₃/H₂O₂/McCN

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>Product (yield, %)</th>
<th>Recovery (%)</th>
<th>Mass balance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2α (40.0) 3a (1.1)</td>
<td>4a (19.8) 5a (4.7) 6a (8.4)</td>
<td>22.6</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b (36.5) 3b d</td>
<td>4b (23.1) 5b (4.8) 6b (6.1)</td>
<td>24.7</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c (33.1) 3c d</td>
<td>4c (15.7) 5c (3.3) 6c (3.4)</td>
<td>19.9</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2d (39.3) 3d d</td>
<td>4d (22.0) 5d (0.7) 6d (1.9)</td>
<td>19.8</td>
</tr>
</tbody>
</table>

* The iron complex Fe(III)₃ (B) can be prepared conveniently by the reaction of Fe(III)(ClO₄)₃·9H₂O (1 mol) with sodium picolinate (3 mol) in water in 93% yield, followed by recrystallization with MeOH, changing it to the hydrous form, Fe(III)₃(H₂O) (A). By exposure to moisture in air, it exists as a mixture of the hydrous and anhydrous form in wet MeCN. Typical reaction procedure: to a solution of substrate (1 mmol) and Fe(III)₃ (0.5 mmol) in MeCN (70 ml) were added three 0.1s-ml portions of 30% aqueous H₂O₂ (0.3 ml, 3 mmol) every 30 min at room temperature and the reaction mixture was stirred for 3 h at room temperature. Isolated yields based on substrates (1). Trace amounts (<0.5%).
Chart 3. Proposed Mechanism for 7α-Hydroxylation of Δ5-Steroids

The mechanism of stereoselective 7α-hydroxylation for the formation of 2 can be postulated to be as follows (Chart 3). The σ bond formation between the C-7α-position in 1 and FeVI atom in (E) as a hypothetically active species with nonradical pathways9 may take place stereoselectively to yield 7 under the stereoelectronic effect9 and steric hindrance. Further, the cleavage of the σ bond between the Fe atom and the C7-position in 7 including the rearrangement of the hydroxy group, may proceed to permit 2 to retain its configuration. On the other hand, the possibility of participation of an active species FeV=O (D) in 7α-hydroxylation cannot be excluded.

Subsequently, we investigated the reaction of 1a with the Gif system (GoAgeIII; FeCl3, 6H2O-PAH/H2O2/HOAc/pyridine) to compare it with the reaction with this modified system. Although reaction of 1a with the above Gif reagent system gave only a 7-oxo derivative 4a in 4% yield, it did not proceed for 7-hydroxy derivatives 2a and 3a.

Furthermore, it was reported that the reactions of cholesterol acetate 1a using known the allylic acetoxylation reagents, CuBu/tert-BuOOCOPh/HOAc,21 Pd(OAc)2Fe(NO3)3·9H2O/O2/HOAc,6 and Pb(OAc)2/HOAc7 gave 3β,7α- and 3β,7β-diaceetoxy-5-cholestenone in almost same amount as the α and β forms, with about 20% yields.

These results provide a new example of oxidative 7α-hydroxylation of Δ5-steroids, one of the major metabolic reactions catalyzed cytochrome P-450, in this model system for mono-oxygenase.

REFERENCES

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