Chemoselective RuO$_4$ Oxidation of Phenyl or $p$-Methoxyphenyl Groups to Carboxylic Acid Functions in the Presence of a Tetrahydropyran Ring

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Received 8 March 2004; revised 13 April 2004

**Abstract:** We describe the first example of a chemoselective oxidation of phenyl and $p$-methoxyphenyl groups to carboxylic acid functions in the presence of a tetrahydropyran ring, using 0.02 mol% of RuCl$_3$ and a co-oxidant. The use of NaIO$_4$ as co-oxidant in H$_2$O–CH$_3$CN–CCl$_4$ as the solvent system led to diketone 7. The change of the co-oxidant from sodium periodate to periodic acid and removal of water from the solvent system led to carboxylic acid 2 in good yield as the sole product.

**Key words:** oxidation, catalysis, aromatic, ruthenium tetroxide, tetrahydropyran, Prins reaction, Barbier reaction

Ruthenium tetroxide has long been known as a vigorous oxidant, capable of readily cleaving carbon-carbon double bonds and aromatic groups.$^1$ The reaction can be carried out with catalytic amounts of RuO$_4$ which is neither explosive nor poisonous and therefore has advantages over the ozonolysis reaction.$^2$ Due to the economical and practical advantages of working with aromatic substrates,$^3$ the use of phenyl groups has been suggested as a synthetic precursor for the carboxylic acid functionality.$^4$ Synthetic protocols based on the ruthenium(III) chloride/NaIO$_4$ oxidation, where RuO$_4$ is prepared in situ, have been published.$^3$ However, the generality of the method is far from that expected for its use because only a few functional groups resist this oxidative process. For example, tetrahydropyrans and tetrahydrofurans are commonly converted to lactones.$^5$ That is, the use of RuO$_4$ oxidation is an efficient synthetic protocol to convert 2,6-dimethyltetrahydrofuran to 2,5-hexanedione and tetrahydropyran to 1,5-pentanodioic acid.$^6$

In this paper, we describe a chemoselective oxidation of the phenyl and $p$-methoxyphenyl groups to the carboxylic acids of (+/–)-2,4,6-$cis,cis$-4-chloro-2-ethyl-6-phenyl-tetrahydropyran (4) (Scheme 1) and (+/–)-2,4,6-$cis,cis$-4-chloro-2-ethyl-6-phenyl-tetrahydro- pyran (6) (Scheme 2). This was done with the aim to prepare the chlorinated acid 2 (Figure 1), a precursor of the tetrahydropyran acid 1, recently described as a new structure class having analgesic properties.$^8$

**Scheme 1** Synthesis of (+/–)-2,4,6-$cis,cis$-4-chloro-2-ethyl-6-phenyl-tetrahydropyran (4).

The Prins cyclization is highly diastereoselective for the preparation of tetrahydropyran skeletons, leading to tetrahydropyrans 2,4,6-$all-cis$-substituted.$^{10}$ The relative $cis$ stereochemistry between $C_2$ and $C_4$ in 4 was confirmed through the coupling constant between the benzylic hydrogen and the CH$_2$ group in C$_3$ ($J = 11.3$ Hz and 2.1 Hz, Figure 2 left side) as well as between the hydrogen on the carbon C$_4$ and the CH$_2$ in C$_3$ ($J = 12$ Hz and 4.5 Hz, Figure 2, right side), which are consistent with these hydrogens occupying the axial position.

The product 6 could not be obtained via the Prins reaction between the allylated product of $p$-methoxybenzaldehyde and propanal, probably due to the Oxonia-Cope rearrangement.$^{11}$ On the other hand, this compound was ef-
ficiently prepared through the Prins reaction between p-methoxybenzaldehyde with hex-5-en-3-ol (5) (70%), which was obtained by a Barbier reaction between propenal and allylbromide in 74% yield (Scheme 2).

The substrate 4 was submitted to the ruthenium tetroxide mediated oxidation using RuCl₃/co-oxidant under various conditions and the results are summarized in Table 1. The use of Sharpless protocol for the ruthenium tetroxide mediated oxidations led to the formation of product 7 derived from the oxidation of the tetrahydropyran ring (entry 1). When the co-oxidant was changed from sodium periodate to periodic acid, a 1:1 mixture of the desired acid 2 and the diketone 7 was obtained (entry 2). In the water-free solvent system and when periodic acid was used as co-oxidant, product 2 was chemoselectively obtained (entries 4 and 5). Under strictly anhydrous conditions an improvement in the chemoselectivity of the product 2 over 7 could be also obtained (entry 6, 52% yield). No reaction was observed with sodium periodate as co-oxidant, under anhydrous condition (entry 3), due to the insolubility of sodium periodate in the water-free solvent system. In view of increasing the chemical yield, substrate 6 was oxidized in place of 4 leading to the desired product 2 only (72% yield, entry 7).

The use of periodic acid in place of sodium periodate as co-oxidant has already been reported in the literature. Its use is justified by the fact that it keeps the reaction media homogeneous, while the sodium iodate formed by reduction of sodium periodate, precipitates and often stops the catalytic cycle (Figure 3). This may lead to a removal of ruthenium salts from the solution, leading in some cases to poor yields. Periodic acid is also advantageous in the present case because it is soluble in the water-free solvent system, making it the co-oxidant of choice for the anhydrous conditions used.

![Figure 2](image)

**Figure 2** Relative stereochemistry of (+/-)-2,4,6-cis,cis-4-chloro-2-ethyl-6-phenyl-tetrahydropyran (4).

![Scheme 2](image)

**Scheme 2** Synthesis of (+/-)-2,4,6-cis-4-chloro-2-ethyl-6-(4-methoxyphenyl)-tetrahydropyran.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Solvent system</th>
<th>Co-oxidant</th>
<th>2:7&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H₂O–CH₃CN–CCl₄</td>
<td>NaIO₄</td>
<td>0:100</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>H₂O–CH₃CN–CCl₄</td>
<td>H₅IO₆</td>
<td>50:50</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>CH₃CN–CCl₂</td>
<td>NaIO₄</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>CH₃CN–CCl₂</td>
<td>H₅IO₆</td>
<td>67:33</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>CH₃CN–CCl₂</td>
<td>H₅IO₆</td>
<td>75:25</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>CH₃CN–CCl₂</td>
<td>H₅IO₆</td>
<td>87:13 (52%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>p-MeOPh</td>
<td>CH₃CN–CCl₂</td>
<td>H₅IO₆</td>
<td>100:0 (72%)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Analyzed by capillary gas chromatography mass spectrometry.
<sup>b</sup> CH₃CN distilled from CaH₂ prior to use.
<sup>c</sup> Strictly anhydrous conditions were used.
<sup>d</sup> Chemical yields of 2 after purification by column flash chromatography.
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The mechanism of ruthenium tetroxide mediated oxidation has been extensively investigated for conversion of ethers to esters \(^{14} \) (Scheme 3) but rarely for olefins \(^{2} \) and aromatic groups. \(^{15} \)

In RuO₄ mediated oxidation reaction of ethers, it has been demonstrated that the kinetics of the reaction is related to the water content of the reaction medium. Such sensitivity varies with the reaction conditions ranging from 5 times to \( 10^6 \) times faster in the presence of water. \(^{14} \)

**Scheme 3** Synchronous mechanism for the ether oxidation by RuO₄.

An already proposed synchronous mechanism \(^{14} \) does not lead to carbocationic character in the transition state (Scheme 3). On the other hand, an ionic mechanism is more appropriate to explain the effect of water in the reaction rate. Carbocationic character of the transition state at the slow step can be suggested (Scheme 4), instead of a complete concerted mechanism, due to the anchimeric assistance of the adjacent oxygen atom as well as the adjacent phenyl group at carbon 2. Steric effects could also play a role in inhibiting the synchronous mechanism due to the usually high entropy of activation for these reactions. The oxidation would then afford a ketal intermediate, which would furnish the diketone 7. This transition state, for the production of the diketone 7, could be a low energy one, due to the solvation by the water present in the solvent system. The presence of periodic acid as the co-oxidant could also lead to a lower aqueous activity, which would slow the tetrahydropyran oxidation rate, allowing the preferential phenyl group oxidation (Table 1, entry 7).

In conclusion, we have observed the first efficient chemoselective example, which converts phenyl and \( p \)-methoxyphenyl groups to carboxylic acids in presence of the tetrahydropyran moiety.

The increasing removal of water from commercial CH₃CN and CCl₄ (Table 1, entry 4), to anhydrous CH₃CN (entry 5), and complete anhydrous conditions (entry 6) was fundamental to the chemoselective oxidation of the phenyl and \( p \)-methoxyphenyl groups over the tetrahydropyran ring due to a decreasing rate of tetrahydropyran oxidation with the anhydrous conditions.

The presence of the \( p \)-methoxy group (electron-releasing group) in 6 improves the aromatic oxidation, over the tetrahydropyran ring, which leads to an increased chemoselectivity and chemical yield.

Finally, the chloro derivative of the analgesic acid 1, 2 (4-chloro-6-ethyl-tetrahydro-pyran-2-carboxylic acid), was prepared in good yield, using a simple and cheap oxidative protocol.

**Typical Procedure**

In a dry round bottom flask were placed periodic acid (1.8 g, 7.9 mmol), and anhyd CH₃CN (7 mL, freshly distilled from CaH₂), with vigorous stirring until dissolution occurred. A solution of 3 (194 mg, 0.86 mmol) in anhyd CCl₄ (7 mL) was then added followed by the addition of ruthenium trichloride trihydrate (0.4 mg). The mixture was left stirring for 24 h at r.t, and the solvent evaporated under

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**Figure 3** Proposed catalytic cycle for the RuO₄ mediated oxidation of organic substrates.

**Scheme 4** Proposed mechanism for the oxidation of the tetrahydropyran ring of 4.
reduced pressure. The residue was re-suspended and filtered through a small column of silica gel with 3% EtOAc in hexane followed by elution with 5% MeOH in CH₂Cl₂. After evaporation of MeOH–CH₂Cl₂, the mixture was purified by flash chromatography, yielding 86 mg (52%) of 2 as a light yellowed oil that solidified upon standing.

1-Phenyl-but-3-en-1-ol (3)\textsuperscript{16}

IR (neat): 3385, 2968, 2937, 2880, 1716, 1463, 1149, 1116 cm\textasciicircum{-1}.

Hex-5-en-3-ol (5)

1H NMR (200 MHz, CDCl\textsubscript{3}): \( \delta = 2.1 \) (s, OH, 1 H), 2.2 (m, 1 H), 2.6 (m, 1 H), 3.3 (m, 1 H), 4.0 (m, 2 H), 6.0 (br s, 1 H).

13C NMR (50 MHz, CDCl\textsubscript{3}): m/z 74.6, 78.4, 173.0.

MS (EL, 70 eV): \( m/z (\%) = 156 \) (0.9) \( [M^+ \text{ – HCl}] \), 138 (8.9), 127 (15.1), 111 (100), 99 (40), 81 (58), 55 (74).

Anal. Calcd for C\textsubscript{8}H\textsubscript{13}ClO: C, 49.88; H, 6.80; O, 24.92. Found: C, 49.76; H, 6.74; O, 25.02.

Acknowledgment

We thank Capes and CNPq for financial support.

References


(16) L. S. M. Miranda, M. L. A. A. Vasconcellos

Synthesis 2004, No. 11, 1767–1770 © Thieme Stuttgart - New York