Substitution of the Benzylc Position of Quinoline Pyrimidinetrione (QPT) Antibacterial Agents

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Introduction

Quinoline pyrimidinetrione or QPT antibacterial agents, exemplified by PNU-286607, are a novel and promising class of antibiotics. This project focused on modifying the benzylc position (highlighted) of the QPT core ring system, an area that has not been previously explored in great detail. Some fine-tuning of the activity profile of the targeted analogs was also planned by varying the substituents \( R_1 (\text{NO}_2, \text{F}) \), \( R_2 (\text{H}, \text{F}) \), and \( R_3 (\text{H}, \text{F}) \). Several advanced intermediates were, in fact, prepared. Two of these intermediates were then used in our initial attempts to substitute the benzylc position.

Synthesis of Advanced Intermediates

The synthesis of the targeted advanced QPT intermediates involved two steps. The first step was incorporation of a morpholine ring via nucleophilic aromatic substitution.

The second step involves condensation of barbituric acid with the aldehyde, followed by cyclization to the requisite QPT core ring system via a [1,5]-hydrogen shift.

2. Barbituric Acid Mediated Cyclization

Cyclization of the above synthesized compounds with barbituric acid (BBA) often proceeded in good yield. In other cases, incomplete conversion to the desired thermodynamic product was observed. Removal of the kinetic product impurity (not shown) by either flash chromatography or recrystallization was generally problematic. Regardless, multigram quantities of compounds 1-3 were obtained.

The QPT analogs 1 and 2 were selected for our initial oxidation studies.

1. Nucleophilic Aromatic Substitution

Using a variety of starting aldehydes or ketones we were able to isolate good yields of the desired morpholine adducts. A mixture of regioisomers was obtained for 2,3,4-trifluoroacetophenone.

<table>
<thead>
<tr>
<th>Aldehyde or Ketone</th>
<th>Amine</th>
<th>Product</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde/acetone</td>
<td></td>
<td></td>
<td>79.80%</td>
</tr>
<tr>
<td>Acetaldehyde/acetone</td>
<td></td>
<td></td>
<td>96%</td>
</tr>
<tr>
<td>Acetaldehyde/acetone</td>
<td></td>
<td></td>
<td>87.97%</td>
</tr>
<tr>
<td>Acetaldehyde/acetone</td>
<td></td>
<td></td>
<td>41%</td>
</tr>
</tbody>
</table>
| Acetaldehyde/acetone |       |         | 67% (3:1 mixture of \( \alpha- \) and \( \beta-\)) |}

3. Benzylc Oxidations Conditions Examined

Oxidation conditions examined:

- KBr, Oxone\(^{\circledast}\), MeNO\(_2\), 50 °C
- KBr, Oxone\(^{\circledast}\), CH\(_3\)Cl, H\(_2\)O, rt, hv
- KBr, Oxone\(^{\circledast}\), CH\(_3\)CN, H\(_2\)O, 45 °C
- 10% CrO\(_3\) in AcOH, H\(_2\)O, 17-21 °C
- Jones Reagent (CrO\(_3\), H\(_2\)SO\(_4\), H\(_2\)O), acetone

Significant amounts of starting material were recovered in reactions using Oxone\(^{\circledast}\). Extractive workups were challenging due to poor QPT solubility. Chromic acid consumed starting material but provided complex mixtures. Small amounts of new products were obtained but on the whole these reactions are not yet synthetically useful.

4. Benzylc Bromination

One benzylc bromination\(^{\circledast}\) was attempted and yielded an encouraging NMR spectrum. Solubility was again a challenge and further optimization is needed prior to being synthetically viable.

5. \( \alpha \)-Hydroxyacetophenones to Facilitate Benzylc Substitution

The second approach was to synthesize substituted \( \alpha \)-hydroxyacetophenones\(^{\circledast}\) and incorporate them into the QPT scaffold. Initial progress is depicted in the table.

Conclusions and Future Work

We were able to synthesize several advanced QPT intermediates, although the second step needs further optimization. The direct oxidation of the benzylc position proved synthetically challenging. The benzylc bromination appeared to be successful, but requires additional refinement. The preparation of selected \( \alpha \)-hydroxyacetophenone starting materials was achieved but needs further optimization before further elaboration into QPT analogs.

References


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